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ORIGINAL ARTICLES.

PATHOLOGICAL CHANGES PRODUCED BY GASTRECTOMY IN YOUNG SWINE.*

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For a number of years Petri and coworkers[6a,b,8–12] have studied the anemia produced in adult dogs following total extirpation or elective resections of the stomach and the proximal part of the duodenum. The original purpose of these experiments was to produce a macrocytic anemia in the experimental animals, but thus far the resulting anemia has been limited to the microcytic variety. When extirpation was limited to the pylorus and the proximal part of the duodenum a non-fatal condition was produced which showed a tendency to remission. These animals showed, as a rule, only large and sharply defined areas of complete loss of hair on the trunk (reminding one of alopecia areata) with pronounced pigmentation of the skin. Achylia and simple anemia were noted. However, when the ventriculus plus the portion of the duodenum containing Brunner's glands was removed in 8 pups (5 to 6 months old) we observed in each a characteristic clinical and pathologic picture. To summarize, these puppies developed extreme emaciation with arrest of growth, salivation, calcium want, coprophagy, muscular atrophy, change in posture (adduction of hind legs, rounded back) and stiff wobbling gait, and a marked degree of simple anemia. In

* These studies were carried out with the aid of a grant from the Michaelsen Fund.

addition, there developed marked changes in the skin consisting of symmetrical loss of hair, a scaly eczema-like hyperkeratosis, and slight pigmentation. On the other hand, the appetite and defecation were normal. Death occurred as a rule within 4 to 12 months, but 1 animal lived for 19 months. The anatomic lesions consisted of nerve cell degeneration in the central nervous system, spinal ganglia and peripheral nerves, hypoplasia or even aplasia of the bone marrow, and moderate hyperplasia of lymph glands.

This clinical and pathologic picture bears so much resemblance to chronic fatal human pellagra that we have provisionally designated it as "experimental chronic pellagra from extirpation of the stomach" in the dog.

The course of the disease in these animals was not influenced by the daily administration of 10 gm. of yeast extract plus 12 to 18 gm. of "ABC-D inmalt."* On the other hand, the administration of human gastric juice alone gave a prompt improvement in the condition of the animal (especially in the skin). These observations, we believe, demonstrate the presence of an "intrinsic" gastric factor in the puppies necessary for maintaining a normal skin and nervous system.

Experiments[7] were then devised to test this observation in man. A group of patients having chronic endogenous pellagra or "alcoholic" polyneuritis were selected whose condition failed to improve when given an abundant diet plus the oral administration of vitamin B-complex preparations. When human gastric juice (100 cc. 3 times daily), press juice of swine stomach (80 cc. 2 times daily), or a preparation of dried swine stomach (Ventriculin, MCO) was substituted for the vitamin B-complex preparation a rapid clinical recovery resulted except in the mental symptoms.

At about the same time similar therapeutic observations in patients with pellagra or polyneuritis have been carried out respectively by Sydenstricker and collaborators[13] and by Douthwaite,[3] who obtained similar results by administration of human gastric juice in their patients. Thus our view concerning the absence of an "intrinsic gastric factor" in some patients having pellagra and related conditions, based originally on animal experiments, has found support not only in our own observations but in clinical investigations by other observers.

From the findings of our previous experimental and supplementary clinical-therapeutic studies, plus the investigations of Sydenstricker *et al.*, and Douthwaite, we think that the presence of a special factor in the stomach required to maintain a healthy skin and nervous system has been demonstrated in dog and man. Particulars as to its nature and mechanism are not yet definable, although it may prop-

* Preparation manufactured by Ferrosan, Ltd. (Copenhagen), containing 1680 internat. units vitamin A, 30 internat. units vitamin B_1, 4 internat. units vitamin B_2, 80 internat. units vitamin C, and 120 internat. units vitamin D per 12 gm.

erly be designated as a "P" factor. We have found it reasonable to identify it entirely or in part with neuropoietin, one of the components of the antipernicious anemia principle, and consequently to regard some of the clinical symptoms and pathologic-anatomical changes in Addisonian pernicious anemia as etiologically and qualitatively identical with pellagra and polyneuritis. Whether it be justified to group these affections as one neurocutaneous symptom complex is a question that will have to be settled by further clinical and therapeutic investigations.

Because of the therapeutic efficacy of swine stomach preparations in the above mentioned diseases, and in view of our previous experimental results obtained in puppies, it seems natural to expect that swine would prove particularly suitable subjects for further experimentation along these lines.

Studies on gastrectomized swine have been reported by Bence,[1] Maison and Ivy,[5] Goodman and collaborators,[4] and lastly by Waterman and collaborators,[14] aiming chiefly at clinical changes in the hemopoietic system in the direction of pernicious anemia. No skin or nervous signs or symptoms were reported. In our experiments, these changes of the skin and in the nervous system only occurred when the operation was performed in puppies. Therefore we have repeated these experiments in Danish "bacon-swine." The purpose of this study is to demonstrate experimental effects of removal of the "P" factor in another animal than the dog, and compare the pathologic picture produced with similarly produced lesions in the dog and with lesions of pellagra and related conditions in man.

Experimental Conditions. The entire stomach was removed, and esophago-jejunostomy was performed in the swine. At the time of the operation these swine were 6 weeks old. The 6 control and 6 test animals were given the same unrestricted diet plus 12 to 18 gm. of "ABC-D inmalt" and 5 gm. of cod-liver oil daily.

Course of Illness. The animals operated upon appeared normal during the first 1 to 2 months. The appetite was excellent and defecation was normal. Within a couple of months after the operation various changes developed. The pigs showed signs of intense universal itching. They ate the cement of the pen in which they were confined (calcium want?). A pronounced inhibition of growth gradually assumed the character of complete arrest of growth, finally becoming extreme emaciation (Fig. 1). The hair of the animals was lost in part, the remaining hairs became long, and lost its lustre, reminding one of sheep's wool; a layer of brownish oily material was deposited on the skin. In some cases, the skin showed flat, rather large, warty plaques; but, in contrast to the previous experiments on dogs, pigmentation of the skin was not observed, perhaps because the pigs were penned up with but little access to the open air. The shape, posture and gait of these pigs were grad-

ually altered; the hind legs appeared relatively long, the back was markedly bent, and the gait became stiff and staggering. There appeared to be some muscular atrophy of the extremities. In the last months of the experiment there was a pronounced involvement of the central nervous system, manifesting itself by almost permanent fibrillary twitchings, contractures of the extremities, localized spasms, and almost ataxic gait. Diarrhea developed terminally. There further appeared a very severe degree of microcytic hypochromic anemia. Hyperglobulinemia was demonstrated in 2 animals. The animals died suddenly, sometimes following a brief period of somnolence, after an observation period ranging from $13\frac{1}{2}$ to $17\frac{1}{2}$ months. In these experiments, the fully developed chronic disease was not influenced in general by administering liver extract* intramuscularly or by stomach preparations *per os*. Following administration of these preparations, as reported in a previous paper, a pronounced reticulocyte response was noted which was not followed by improvement in the degree of anemia.

Pathologic-anatomical Changes. On autopsy, these animals presented in composite a large number of changes, forming a rather varied picture.

The common macroscopic changes observed include arrest of growth, anemia, emaciation, complete loss of adipose tissue, moderate muscular atrophy, and changes in the skin, involving loss of hair. In addition, there was atrophy of the thyroid, and slight chronic inflammatory changes in the mucous membrane of the tongue. The site of the esophago-jejunostomy had healed well, presenting no dilatation, nor any remnants of gastric mucosa worth mentioning.

The microscopic changes in the nervous system of the gastrectomized pigs were qualitatively alike, but quantitatively variable. They were conspicuous in the central nervous system and the spinal ganglia (Fig. 2), but less pronounced in the peripheral nerves. The changes consisted of various degenerative phenomena in the nerve cells, *e. g.*, vacuolization of the protoplasm, alteration of the Nissl structure, eccentric position of the nuclei, or even karyorrhexis. In the nerve fibers the myeline degeneration was of a diffuse character but of slight degree. Finally, there was a conspicuous dilatation of the small blood-vessels (Fig. 3) with thickening of their walls. These findings, on the whole, corresponded to those found in gastrectomized puppies.

In a majority of these animals the spleen had undergone atrophy. The lymph glands contained a good many plasma cells or eosinophil leukocytes, but were not enlarged. The bone marrow was gelatinous, red in color (in the femur) or grayish-yellow (in the tibia). On microscopic examination, the marrow was found to be markedly

* Hepsol Fortior, manufactured by Medicinalco, Ltd. (MCO), Copenhagen.

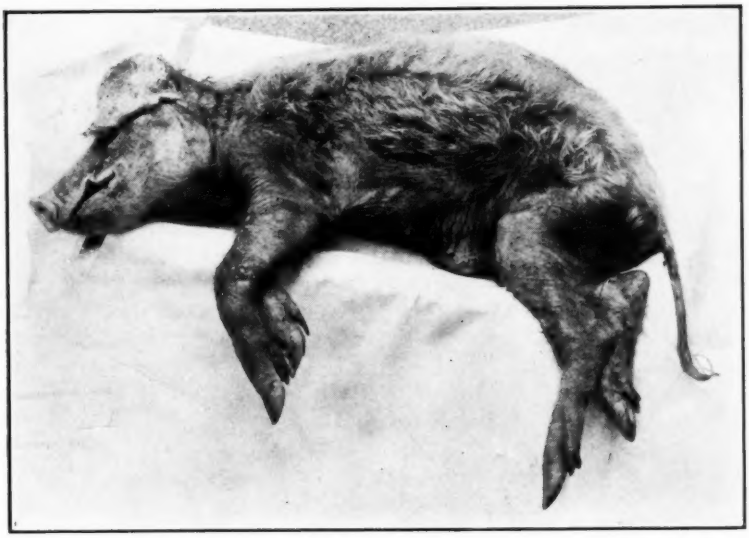

FIG. 1.—Swine, 19 months old. Total gastrectomy at age 6 weeks. Observation period 17½ months. Weight, 16 kg. Length of trunk, 65 cm.

FIG. 2.—Spinal ganglion from gastrectomized swine.

FIG. 3.—Spinal cord of gastrectomized swine, showing dilatation and thickening of central blood-vessels.

edematous, with dilatation of the blood-vessels. The number of cells in the marrow was variable in the individual animals; the femur showed a "fat" marrow rich in cells, while the marrow of the tibia was almost free from specific cells. The number of specific bone-marrow cells was rather scanty, with a distribution corresponding to that observed in adult animals. Nucleated red cells were relatively few in number.

A minority of these animals, on the other hand, presented a moderate or marked hyperplasia of the spleen and lymph glands. These organs showed a marked plasma-cell metaplasia and a more scanty number of myeloid elements. In 1 animal, the bone marrow was the site of diffuse fibrosis with scattered small islands of marrow cells; another animal showed a diffuse marked hyperplasia of the bone marrow, though without any pronounced predominance of nucleated red cells. The latter animal showed also cirrhosis of the liver, of "Hanot's" type. It was in the 2 latter animals that hyperglobulinemia was encountered, and in these the inhibition of growth was distinctly less pronounced than in the other animals.

Finally, other special changes were seen in 1 or more of the 6 animals in this group, namely: tendency to transudation (subcutaneous edema, hydrothorax, ascites), hypertrophy of the heart, hyaline degeneration of the glomeruli of the kidneys, cellular infiltrations (presumably myeloid) in the testis and liver (partly with beginning cirrhosis?), hyperkeratosis, and marked osteoporosis.

Discussion. By removal of the stomach in young pigs it is possible to produce a number of diverse, severe, clinical and pathologic-anatomical changes. The picture is characterized in particular by arrest of growth, skin changes, hypochromic microcytic anemia, and degenerative changes in the central nervous system.

The present experiments have afforded an additional proof of the far-reaching significance of the stomach to the organism, especially during growth, indicating the presence of a specific "P" factor in the stomach concerned with maintaining a healthy skin and nervous system. Whether, for instance, the coincident abolition of the hydrochloric acid production directly or indirectly plays a part in the development of some of the diverse changes here observed is a question that remains open for the present. In their features and course, the changes observed in our pigs deviate in nearly every respect from the findings reported by other investigators in experiments with a similar technique. This difference no doubt is attributable to the young age of our pigs at the time of the operation.

Young pigs, like ours, may safely be characterized as suitable experimental subjects for further studies on the relation of the stomach to the changes in the skin and nervous systems, as in pellagra, and may supplement our knowledge of the relation of the stomach to pernicious anemia, as well as on the pathogenesis and possible

etiologic explanation of several of the concomitant phenomena here observed. In addition, the experimental and clinical-therapeutic studies we have carried out thus far illustrate the general risk to the organism that may be involved in extensive resection of the stomach, especially in relatively young patients.

The condition of hyperglobulinemia with preponderant plasma-cell metaplasia of the spleen and lymph glands as observed in 2 of our animals lends experimental support to the hypothesis advanced by Bing and Plum[2] concerning the causal aspects of the hyperproteinemias. Finally, in view of the reticulocytic reaction which the animals have shown to administration of liver and stomach preparations, as mentioned in a previous paper,[9] our experiments suggest the possibility of elaborating a biologic method for determination of the potency of "antipernicious" preparations and their possible variations in action.

Summary. Operative removal of the stomach in 6 pigs, 6 weeks old, gives rise to a number of severe clinical and pathologic-anatomical changes that may be interpreted as phenomena similar to those found in human pellagra. Conspicuous features in this condition are arrest of growth, hypochromic microcytic anemia, and extensive changes in the skin and in the central nervous system. In addition, there were inconstant diverse changes, as hyperproteinemia, plasma-cell metaplasia of the spleen and lymph glands, cirrhosis of the liver, osteoporosis, and other phenomena.

In principle, the results of these experiments correspond to our findings in previous studies on pups, further suggesting the presence of a specific factor in the stomach of swine, dog, and man which is required to maintain the skin and central nervous system in a normal healthy state.

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OBSERVATIONS ON THE ETIOLOGY OF THE TOXEMIAS OF PREGNANCY.

IV. THE PRIMARY ROLE OF THE PLASMA PROTEINS IN CONDITIONING WATER RETENTION AND EDEMA FORMATION IN NORMAL AND "TOXEMIC" PREGNANCY.*

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THE importance of water retention in "toxemia" of pregnancy has been previously emphasized.[6a,b,c] This condition is, of course, to be differentiated from vascular or renal disease associated with pregnancy. It has been pointed out that "toxemic" manifestations may be relieved by decreasing water retention[6a] or exaggerated by inducing further water retention.[6b]

Previous observations[6a,b,c] indicated that the chief factor responsible for water retention in pregnancy is a lowering of the colloid osmotic pressure of the plasma due to hypoproteinemia. However, in view of the rather widely held beliefs that water retention in pregnancy depends upon hormonal[1] or renal[9] disturbances, the present study was undertaken to establish conclusively that it is the plasma protein level which is the primary and most important factor involved in water retention in both normal and "toxemic" pregnancy.

The presence or absence of gross edema is an extremely crude measure of water retention. It is well known that one individual may show visible edema following the retention of only 2 or 3 kg. of water, whereas another patient may conceal in the body tissues 5 or 6 kg. of retained water. The literature contains many references to a so-called critical level of the plasma proteins, below which edema occurs. The recent studies of Weech and his associates,[7] however, indicate that water retention proceeds uniformly *pari-passu* with the decline in the plasma-protein level of dogs on protein-deficient diets and that the first appearance of manifest edema is not associated with any sudden or marked increase in water retention.

The evidence in favor of hypoproteinemia as the chief cause of water retention in pregnancy may be summarized at this point. 1, The amount of water retained by pregnant women during the administration of sodium salts[6b] is inversely proportional to the colloid osmotic pressure of their plasma proteins.[6c] 2, Pregnant

* This study was aided in part by a grant from the William W. Wellington Memorial Research Fund of the Harvard Medical School.

women with hypoproteinemia, even though they have no manifest edema, lose weight readily ascribable to water loss when placed upon a diet containing daily 260 gm. of protein and an adequate number of calories.[6a] 3, It has been determined by an analysis of data[6a] that the amount of body weight lost is very roughly in inverse proportion to the level of the colloid osmotic pressure of the plasma proteins. The lack of better correlation may be ascribed, among other factors, to the absence of a preliminary period of stabilization following admission to the hospital, to the absence of any control of the salt intake, and to the fact that at the time the observations were made, the chemical methods used to determine the quantitative amounts of plasma albumin and total protein were by no means as uniformly accurate as at present. Further, blood was withdrawn for these determinations on the patient's first day in the hospital, whereas for the data to be presented here it was not taken until the patient had become stabilized as far as fluid exchange was concerned after several days on the hospital ward.

Methods. Twenty women in the last trimester of pregnancy were selected for study. They included 3 normal pregnant women and 1 each diagnosed as having chronic glomerulonephritis, acute pyelonephritis, chronic pyelonephritis and polycystic kidneys; 8 women had essential arterial hypertension and 5 "toxemia" of pregnancy. Upon admission to the ward the patients were placed upon house diets without restrictions of any sort. They were not confined to bed. Salt and water were permitted *ad lib.* No sodium bicarbonate was allowed, nor were saline cathartics permitted, since it has been shown[3] that at least magnesium sulphate may act as an acidifying diuretic in patients with edema. The patients were weighed each morning before breakfast. The arterial blood pressure was measured after the patients had been at rest in a chair for 20 minutes. Blood was not withdrawn for the determination of the plasma proteins until the third or fourth morning in the hospital, when the patient's weight had become relatively constant. The women were recumbent for at least 20 minutes before the blood was withdrawn without stasis from an antecubital vein. The venous pressure was determined at the same time by the method of Moritz and von Tabora. By a micromodification of Howe's method the plasma albumin and the total plasma protein concentrations were determined on blood to which a uniform amount of potassium oxalate had been added to prevent coagulation. It is believed that all of the above precautions are essential if quantitatively accurate results are to be obtained. After the preliminary period of observation was completed each patient received 1500 cc. of skimmed milk daily for 5 days as the only food. Each was encouraged to take whatever water she desired. No limitation or forcing of fluids was permitted. The skimmed milk régime was employed because it was *par excellence* an ideally uniform, low-sodium diet. Other types of low-sodium diets are likely to be unpalatable and therefore variations in food intake (and hence salt intake) occur. Furthermore, none of the patients seriously objected to this régime, nor did disturbing symptoms from lack of food occur. Fifteen hundred cubic centimeters of skimmed milk contain approximately 0.57 gm. of sodium, 2.14 gm. of potassium, 2.14 gm. of calcium and 0.18 gm. of magnesium, together with 53 gm. of protein, 73 gm. of carbohydrate and 10 gm. of fat, with a total of 600 calories. The choice of a low-sodium régime was, of course, based on the previous observation that the administration of sodium in excess resulted in water retention.[6b]

Results. Each of the 20 women lost weight during the period of 5 days when they had only milk. In the chart is shown the percentage of the original body weight which was lost. This was calculated by subtracting the weight on the morning of the sixth day from the weight on the morning of the first day of the skimmed milk régime and dividing the result by the latter weight. The percentage weight loss for each patient has been plotted against the calculated colloid osmotic pressure[8] of that patient's plasma proteins. The correlation is remarkably good, and establishes the primary importance in these 20 women of the plasma-protein level in conditioning water retention. In every instance in which visible edema was present this disappeared. It is, however, worthy of note that some patients without manifest edema lost as much as 8 pounds of weight, apparently water.

In the 12 patients who were diagnosed as having primary vascular or renal disease and in the 3 normal women no consistent effect of that milk régime upon blood pressure, albuminuria, or symptoms was noted. In the 5 patients with "toxemia" of pregnancy, symptoms such as headache and visual disturbances abated, the blood pressures returned to normal and albuminuria decreased. These latter women were placed on a relatively salt-free, 150-gm. protein diet following the skimmed milk régime. Under this therapy they continued to remain free of edema and "toxemic" signs and symptoms. Studies made 6 or more weeks postpartum failed to reveal evidence of vascular or renal disease. On the other hand, the 12 women considered to have vascular or renal disease during pregnancy all continued to show hypertension or urinary abnormalities later.*

Complete data on the relation of water retention to arterial hypertension in pregnancy will be reported at a later date.

Discussion. These 20 patients' food contained daily only 600 calories. One must thus ask how much of the weight loss in 5 days may be ascribed to the burning of body fat. Such loss depends upon the weight of the patient and the total metabolism. The total metabolism of patients at rest on a hospital ward can hardly be more than basal +20%. Pregnancy raises the metabolism by approximately an additional 20%. To insure against underestimation, calculation of the *theoretic* weight loss from the burning of body fat in these patients has been made on a basis of basal requirements +*50%*. Nineteen of these 20 women weighed between 120 and 170 pounds. A 600-calory intake for 5 days should theoretically result in a loss of 1.47% weight in a 120-pound subject and a loss of 1.66% weight in a 170-pound subject from the burning

* Since this paper was submitted for publication 22 additional pregnant women have been studied, 10 of whom had "toxemia" of pregnancy. These 10 women all showed a return of blood pressure to normal and a subsidence of "toxemic" symptoms concomitant with the loss of retained water, while the 12 women with primary vascular or renal disease showed no consistent change.

of body fat. Since the difference is but 0.19%, it is apparent that this factor does not enter into the great differences in the amounts of weight lost by these subjects, and that at most it can account for less than 2% of the total weight loss. Further, these patients showed no tendency to regain their lost weight when placed on sodium-poor but adequate caloric diets. Two patients, not included in this report because they were not placed on the skimmed milk régime, were, however, given relatively sodium-free diets containing adequate calories. Each lost essentially the same amount of weight as did patients on the milk régime with similar plasma osmotic

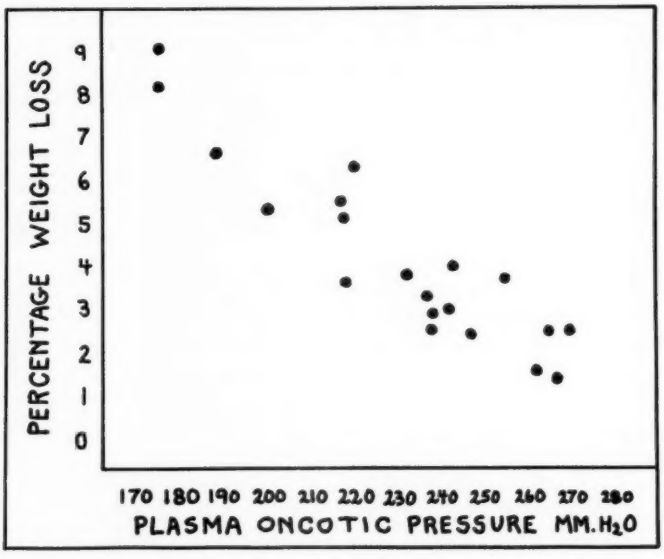

CHART I.—Percentage weight loss in 5 days during the administration of 1500 cc. of skimmed milk daily plotted against the colloid osmotic (oncotic) pressure of the plasma proteins.

pressures. Lastly, 1 patient who lost 6.3% of her body weight on the milk régime was allowed to partake of a house diet with sodium chloride taken freely. After she regained her original weight she was again placed on the milk régime, but with 6.3 gm. of sodium (as the bicarbonate) added. Only 0.9% of weight was lost in this 5-day period.

It is thus apparent that the weight losses observed in these patients represent essentially a loss of retained water, and that the amount lost is a measure of the amount originally retained.

Much has been written concerning the rôle of the pituitary antidiuretic hormone in inducing water retention in pregnancy.[1] More

recently other hormones[4] have been shown capable of causing changes in water metabolism. No proof has been offered which has withstood critical examination that any hormones are involved in water retention in pregnancy. Certainly the data here presented do not require the assumption of hormonal influence. It is known that anemia *per se*, irrespective of the plasma protein level,[5] can condition water retention. One of the patients in this study was observed twice on a skimmed milk régime. During the first period (not included in this report) her hemoglobin was 37% (Sahli) (5.76 gm. per 100 cc.). She lost 8% of her body weight in 5 days and her diffuse generalized edema disappeared. The plasma-protein level at this time was such that the calculated osmotic pressure was 251 mm. of water. Later, when after treatment as an out-patient her hemoglobin was 72% (11.2 gm. per 100 cc.) she returned with a calculated osmotic pressure of 237 mm. of water but no edema. This time she lost only 3.3% of body weight while taking for 5 days a diet consisting only of 1500 cc. of skimmed milk.

It is also well known that hypoproteinemic water retention, both in animals and humans, may not be amenable to therapy either by sodium withdrawal or acidifying diuretics if the level of the plasma proteins is exceedingly low. A patient with "toxemia" of pregnancy and a calculated osmotic pressure of but 150 mm. of water lost only 3% of body weight on the skimmed milk régime and only 1% additional when ammonium chloride[6b] was added. She continued to have generalized edema, hypertension and other toxemic symptoms. Labor was induced. Six weeks later her weight was 38 pounds less, edema absent, blood pressure normal, and urine free of albumin.*

There is no question but that acute glomerulonephritis and probably certain other rare types of renal lesions may result in edema apart from an effect on the plasma proteins. However, acute glomerulonephritis has an incidence of less than 1 in 5000 pregnancies.[2] None of the patients reported here suffered from this condition. Furthermore, the edema fluid of acute glomerulonephritis has a high-protein content whereas the edema fluid of pregnancy toxemias is of low-protein content.

The patients suffering from acute pyelonephritis, chronic pyelonephritis, polycystic kidneys and glomerulonephritis each lost weight in proportion to their plasma-protein levels. It is, therefore, apparent that at least in these 4 patients water retention was unrelated to the renal condition except insofar as the latter affected the plasma-protein level.

An elevated intracapillary pressure brought about through arteriolar dilatation from a lack of vitamin B_1 as in beriberi may be

* Two similar patients have been observed since this paper was submitted.

accompanied by edema. That this is not the cause of edema in pregnancy toxemias has been indicated in the preceding paper.[6c] Likewise an increased intracapillary pressure due to a large increase in venous pressure as in congestive right heart failure may cause edema. Data on patients with heart failure have not been included in this report. No patient had a pressure in the antecubital vein greater than 15 cm. of water.

The rôle of increased venous pressure in the legs during the last trimester of pregnancy in producing local edema is obvious. Many pregnant women will lose weight upon being put to bed and some merely through a restriction of activity, presumably from alteration in the femoral venous pressure. There is no doubt that ambulatory hospital existence represents a definite restriction of activity, but this is of no concern in connection with the observations reported here because the same restriction of activity was present during the preliminary control period.

It is thus apparent that in the absence of severe anemia, congestive heart failure and acute glomerulonephritis, water retention in both normal and "toxemic" pregnancy depends essentially on the level of the plasma proteins and may be influenced, as in non-pregnant patients and laboratory animals, by changes in the intake of electrolytes, chief of which is sodium. Thus, water retention in pregnancy does not differ from water retention in the non-pregnant.

Conclusions. 1. Whether there is manifest edema or not, water retention is nevertheless present in greater or less degree in a large proportion of women during the last trimester of pregnancy. It may amount to as much as 10% of body weight.

2. This water retention is primarily conditioned by the level of the plasma proteins. The amount of water retained is in inverse proportion to the osmotic pressure of the plasma proteins.

3. Unless the plasma proteins are below a certain level, a régime consisting of 1500 cc. of skimmed milk daily, and hence extremely low in sodium but relatively high in calcium and potassium, will result in the elimination of retained water.

The writer is indebted to the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital for their coöperation which made this study possible.

Miss Margaret A. Adams performed the chemical determinations reported in this paper.

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THE SEDIMENTOMETER.

A Photographic Recorder of the Suspension Stability of the Erythrocyte.

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The erythrocyte suspension stability test has long passed the initial experimental stage and is now recognized throughout the world as a routine laboratory investigation of practical service to medical clinics. In many articles favorable reports will be found on its value in tuberculosis,[12] rheumatic carditis,[1] rheumatoid arthritis and allied complaints, syphilis, various infective conditions and gynecologic lesions.[3] Frequent repetition of the test is advisable and it then becomes a reliable indicator of the changing reactions of the patient to infective processes. Thus in pulmonary tuberculosis Trail[11] has found the repetition of sedimentation tests at regular intervals to be of considerable value in assessing the prognosis of sanatorium cases, and other writers[4] have confirmed the abnormal sedimentation rate in afebrile tuberculous patients with slowly progressive disease. It is owing to its extensive use that the erythrocyte sedimentation test has been made as simple as possible by making a single observation at the end of 1 hour's sedimentation. On the other hand, it is realized that to obtain more accurate information it is necessary to take frequent readings. Thus Cutler[2] in particular stresses the importance of observing the rate of sedimentation in the early stages; this he achieves by recording readings every 5 minutes; the results are then recorded in the form of a graph, an impressive picture being obtained of the rate of fall of the cellular element of the blood.

Such a sedimentation test, involving personal readings every 5 minutes, though simple enough to perform, takes up much of a clinician's time, the more so if it is to be frequently repeated. It is not surprising that mechanical devices have been made to record result automatically.[7] But so far as the writer is aware these have not been sufficiently practical to be widely used; thus Sulkowitch[10] devised an apparatus which worked by throwing a shadow outline of the sedimenting blood on sensitized paper mounted on a kinographic drum. Using a somewhat similar apparatus the author was confronted with practical difficulties. As the beam of light traversed the clear plasma layer above the sedimenting blood, diffusion of this light often gave a poorly defined silhouette. In addition, the standardized electric light had to be carefully controlled so that it was necessary to place the apparatus in a light-proof compartment in order to exclude daylight. The instrument was thus made bulky

while the need both of a dark room for loading and of a mechanism for automatic switching off the light at the end of the exposure period added further complications. On the other hand, such an apparatus takes a continuous record from a number of sedimentation tubes. Other investigators[9] now photograph a number of tubes at the end of a convenient time period. This method requires a short focusing camera and a special mechanism for operating the lens shutter. Ride,[8] using a Leica camera, has made an apparatus which takes multiple pictures at 6-minute intervals. Judging from his brief description the mechanism must be costly and in order to obtain consecutive recordings of the individual tubes, each photograph must be read in turn and the results plotted on graph paper. The author has combined both the silhouette and camera methods to produce a compact instrument in which many of the advantages of both methods are included.

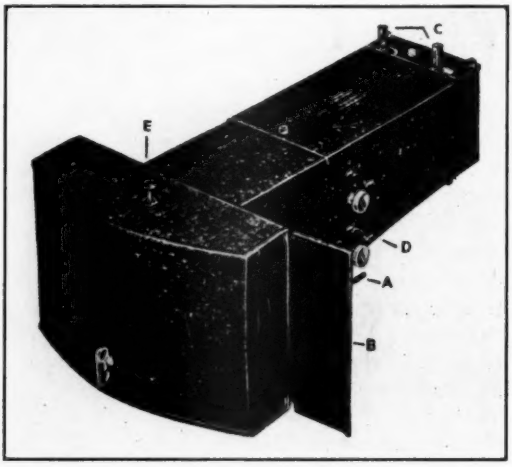

FIG. 1.—The sedimentometer. The photographic plate is loaded through the door (*B*) into the moving stage (which can be seen just to the left of the door). This stage is caused to move by releasing the pin (*E*), and the image of the tubes (*C*) is received on the photographic plate when the shutters (*D*) are opened.

Description of Sedimentometer. As previously described,[5] the new apparatus known as the "sedimentometer" (Fig. 1) actually photographs the sedimentation tube on a moving light sensitive surface. To achieve this, light obtained from any reasonable source, including daylight, passes through a frosted glass window in the sedimentometer. It then falls on a slot holding the sedimentation tube. The light is readily transmitted through the clear plasma layer but is blocked out by the opaque mass of red cells below. Behind the sedimentation tube is a single lens; this throws an image of that part of the tube above the sedimenting cellular layer on to a light sensitive surface behind a narrow vertical slot at the back of the apparatus. On making a short exposure a narrow vertical

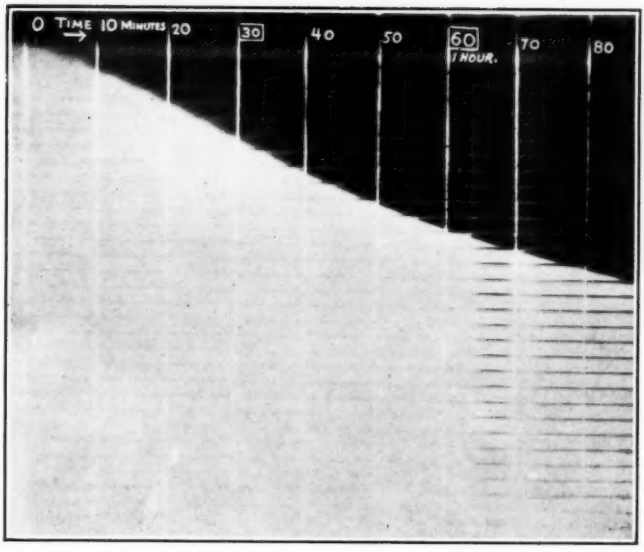

FIG. 2.—Photograph of a sedimentation curve taken over 90 minutes. Sedimentation index, 11 mm.

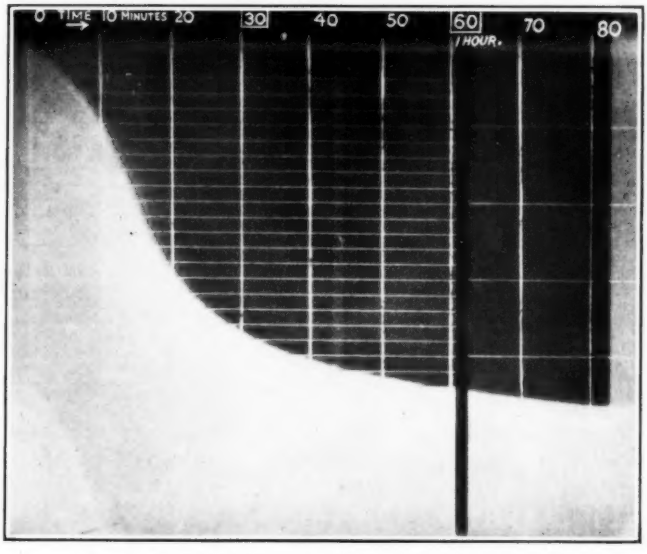

FIG. 3.—A vertical curve. Sedimentation index, 22 mm.

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photograph is obtained. This will show a small free space above the fluid level; immediately below that the meniscus will be seen as a thin white line. Beneath the meniscus is the clear plasma layer with the millimeter graduations of the sedimentation tube showing through. Finally, a sharply defined margin accurately indicates the upper surface of the opaque cellular layer. But to obtain a continuous record of the blood fall, the photographic paper must be mounted on a moving stage. A simple clockwork mechanism drives this stage which carries an ordinary camera-plate holder loaded with photographic paper. Thus in the sedimentometer, coincident with the progressive sedimentation in the tube, sensitized paper will travel past the tube image which can only fall on the paper through the vertical light slot. A continuous and accurate photosedimentation graph is thus obtained. In the standard machine, during the short time required for preparation of the specimen and withdrawal of the covering slide of the plate holder, the movable stage is kept locked at zero position, but on closure of a side-door movement of the stage commences. It then travels at a rate of 60 mm. an hour. The author now records time markings by placing a transparent piece of film in front of the sensitized paper when the plate holders are loaded. Opaque vertical lines are drawn on this film so that every 10 minutes one of these passes the light slot. After development not only are the millimeter graduations of the tube recorded but also these time markings, so that the print is actually a completed graph (Fig. 2). Retouching is therefore unnecessary.

A sedimentometer may be built to record any type of tube, but for compactness, shorter tubes of 50 mm. or less in length are the most suitable. This Cutler technique[2b] has been adopted as a standard. By projecting an image twice the actual size on to a stage moving at a rate of 60 mm. an hour, the photosedimentation curve will conform to the recognized Cutler standards. Speed and magnification can, of course, be varied. In a multiple sedimentometer 4 Cutler tubes can be recorded on quarter plate size paper; then the images would have to be the same size as the tubes and the stage made to travel at the rate of 30 mm. an hour. The resultant curves, though smaller in size, would be proportionally identical with those of the standard sedimentometer. By use of the formula $D = 2/3\ LM$ (where D equals the distance traveled by the stage in an hour, L the length of the tube, and M the magnification) any of the shorter tubes will give approximately the same results. For tubes longer than 50 mm., however, this formula needs slight modification.

Discussion. A comparative study of sedimentation graphs from tubes of different lengths will help to explain the variations of their respective curves. The typical vertical curve of Cutler (Fig. 3), indicating very rapid sedimentation, consists of a short pre-sedimentation period when the fall is very slight, a true sedimentation period of rapid fall, and finally a packing stage when the curve flattens out. In a longer tube the pre-sedimentation period is approximately the same, but the sedimentation period is continued almost throughout the whole hour and to obtain a packing stage proportionate to the Cutler curve, observation must be continued beyond 1 hour. To apply it for longer tubes, the above formula is therefore modified by not only increasing the time of exposure but also by causing the stage to move at a slower speed. In the case of a 100-mm. tube,[13] when using a magnification of 1, the time of exposure should be 90 minutes and in that time the stage should

travel 60 mm. If curves of 50- and 100-mm. columns of the same blood are superimposed in this manner, they will be found more or less to coincide (Figs. 4 and 5). As the pre-sedimentation time is approximately the same in both tubes, the vertical curve in the

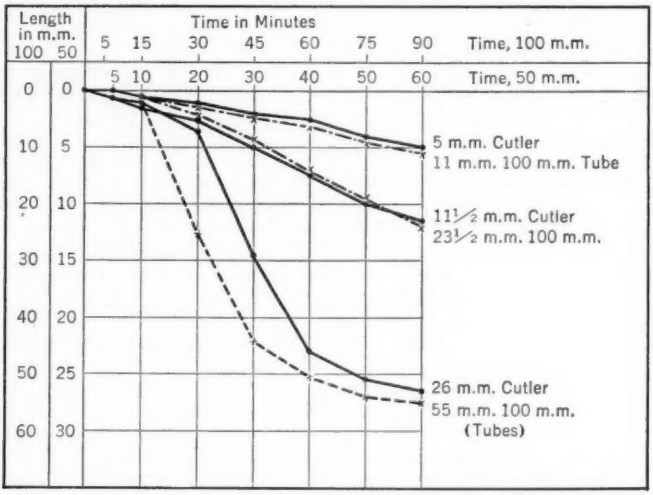

Fig. 4.—Sedimentation curves of three different samples of blood to illustrate text. The unbroken lines represent the 50 mm. curves and the interrupted lines the 100 mm. curves.

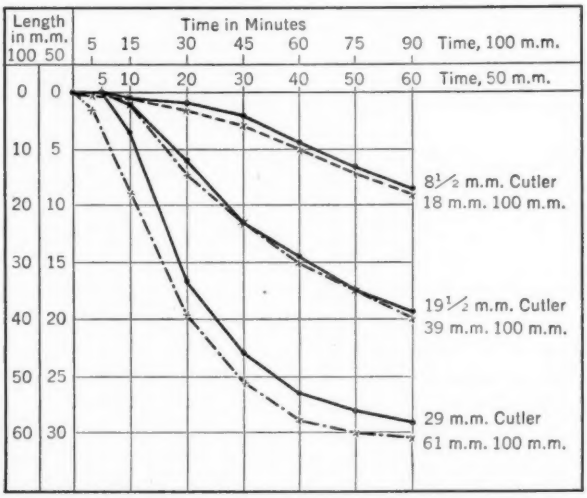

Fig. 5.—Sedimentation curves drawn as in Fig. 4. Note that the 100 mm. vertical curve is here much steeper than the 50 mm. curve.

case of the longer tube will be much steeper (Fig. 5); this should prove rather advantageous. The readings in the graphs shown were obtained by an observer before any such relationship was thought of, and the records are taken at random from a series of 10 samples. It is possible that by further increase of the exposure period any length of tube greater than 100 mm. may also be used. Hitherto there has been much confusion owing to inability to compare the results obtained by different methods, but with the introduction of the sedimentometer, it is possible in most cases to record curves that will conform to those standardized by the Cutler technique. Furthermore, it is hoped that the instrument will be of some value in introducing the erythrocyte suspension stability test as a routine in medical clinics, especially tuberculosis dispensaries. Judging from a small personal series of repeated sedimentation tests performed on over 100 tuberculous patients, all of whom were kept under close supervision (including physical, bacteriologic and radiologic examinations), the Cutler method has been found to correspond accurately to the clinical conditions of the patient. Again and again a fall in the sedimentation curve has been found to herald a bout of activity. Because of this close correlation, the Cutler method has been adopted as a standard in the sedimentometer.

Summary. The value of multiple readings when observing the suspension stability of the erythrocyte is emphasized and the need of an apparatus for automatic recording suggested.

The working principles of such instruments that are at present used in laboratories are briefly outlined. For convenience these are referred to as the silhouette and camera methods.

A new and compact apparatus known as the "sedimentometer" is described. This gives a continuous photosedimentation curve which conforms to recognized Cutler curves. The essential modifications are described to indicate how the sedimentometer may be used to record the suspension stability test in tubes of varying lengths.

The author is indebted to Dr. McDougall, Medical Director of Preston Hall, for permission to use the readings published in this article. He is grateful to Drs. J. C. Crawford and W. E. Fitzgerald, also the Ellis Optical Company (the manufacturers) and others, for their helpful suggestions; and to Messrs. Hawksley & Sons, Ltd., of 17, New Cavendish Street, London, W.1., the distributors of the sedimentometer.

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THE INFLUENCE OF ANEMIA ON BLOOD SEDIMENTATION.*

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For some years there has appeared an increasing number of papers on blood sedimentation, emphasizing the necessity of correcting for anemia to make possible a more accurate evaluation of the sedimentation test. Those who advocate "correction" maintain that anemia materially increases the sedimentation rate, so that the latter reflects not only the activity of the disease but also the cell concentration. They further assume that the anemia factor can be isolated and corrected for by simply subtracting sufficient plasma to bring the volume percentage to 47% or the cell count to 5,000,000 before performing the test. The difference between the sedimentation rate of the corrected and the uncorrected or anemia sample is believed to represent the increased sedimentation brought about by the anemia factor itself. Formulæ have been proposed and graphs and tables constructed in an attempt to simplify the computation of just how much of any particular sedimentation rate is due to the associated anemia.

The present study was undertaken to determine the justification of current efforts to correct for anemia. The answer is best sought in an understanding of the mechanism of blood sedimentation.

Blood Sedimentation and Rouleaux Formation. Although the mechanism of blood sedimentation is only partially understood, certain facts are available. Suitable experiments easily show that the plasma, or the medium in which the cells are suspended, is primarily responsible for the rapid settling, and not the number, size or shape of the erythrocytes. The rate of settling can be controlled at will by altering the suspension medium, thus showing that the cells play only a passive rôle.

When the behavior of settling cells is studied under different conditions the essential difference is that those settling rapidly form large aggregates or rouleaux, a fact emphasized by Fahraeus, Ponder and others, while in slowly settling blood the ability of erythrocytes to form aggregates is slight (Figs. 1 and 2). A reasonable

* Presented before the Section on Medicine of the College of Physicians of Philadelphia, October 25, 1937.

relationship can be established between the degree of rouleaux formation or size of aggregate and the rapidity of sedimentation in blood with intermediate settling (Experiments I to XVI, incl.).

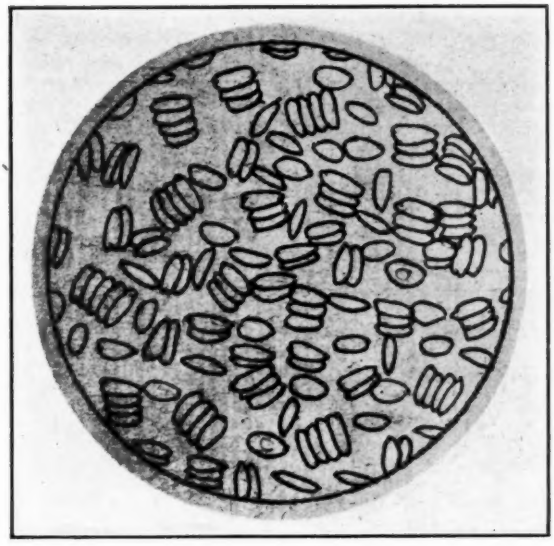

FIG. 1.—Rouleaux formation in slowly sedimenting blood.

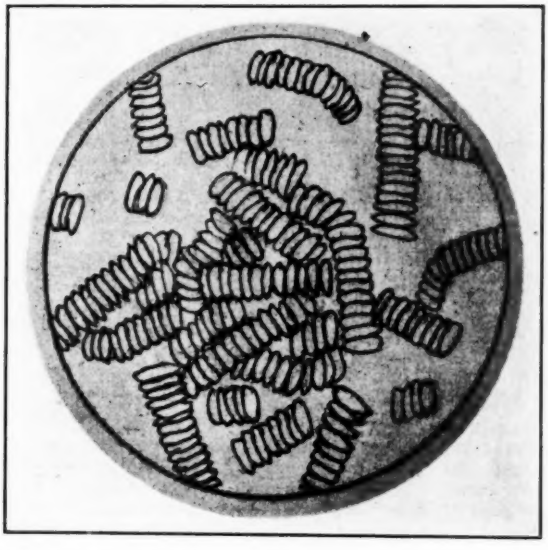

FIG. 2.—Rouleaux formation in rapidly sedimenting blood.

Experiment I. *Interchange of Cells and Plasma.* When cells of slowly sedimenting blood (Fig. 3, *a*) are transferred to plasma of rapidly settling blood (Fig. 3, *b*) they settle rapidly (Fig. 3,*c*); whereas, when cells of rapidly sedimenting blood (Fig. 3 *b*) are transferred to plasma of slowly sedimenting blood (Fig. 3*a*) they settle slowly (Fig. 3 *d*). The number of cells and hematocrit findings, indicated in Figure 3 as volume percentage, are approximately the same in the transferred sample as in the original blood.

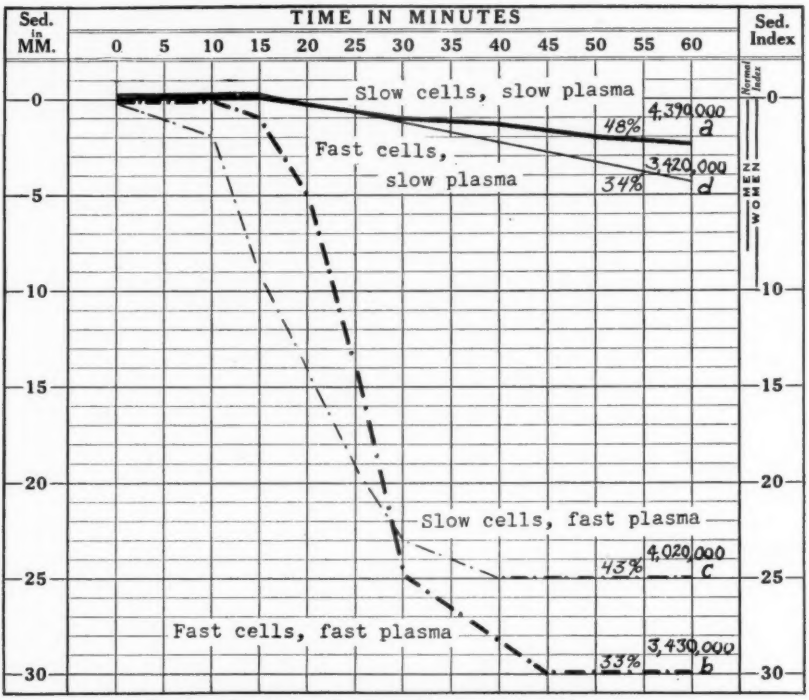

FIG. 3.—Experiment I. Interchange of cells and plasma.

The following table lists the average and the maximum number of cells per rouleaux, and the percentage of cells engaged in rouleaux formation under the different conditions of the experiment.

	Average No. of cells per aggregate.	Maximum No. of cells per aggregate.	% of cells engaged in rouleaux* formation.
Graph A (slow cells, slow plasma) . . .	2	2	5
Graph D (fast cells, slow plasma) . . .	2	2	5
Graph C (slow cells, fast plasma) . . .	20	55	97
Graph B (fast cells, fast plasma) . . .	25	45	90

* With occasional exceptions, all rouleaux studies were made by adding equal parts of saline to the blood and placing this mixture on a glass slide with a cover slip. This procedure uniformly diminished rouleaux formation to a range that facilitated the visual differentiation of the tendency to rouleaux formation of any sample of blood. It was found by trial and error that 50% of saline and 50% of blood was just about the optimum proportion. With a lesser percentage of saline, all bloods form large rouleaux, and are distinguished from one another only with difficulty. On the other hand, if too high a percentage of saline is used, the tendency of all bloods to form rouleaux is very materially diminished or lost.

Experiment II. *Erythrocytes of rapidly sedimenting blood suspended in physiologic salt solution and resuspended in plasma of the original blood.* When the plasma of rapidly settling blood (Fig. 4 *a*) is replaced with physiologic salt solution, there is a progressive slowing in the settling of the red cells (Fig. 4 *b*) until sedimentation is almost inhibited with a dilution of four parts of saline to one part of "fast" plasma of rapidly settling blood (Fig. 4 *c*). When resuspended in the original fast plasma the cells again sediment fast (Fig. 4 *d*).

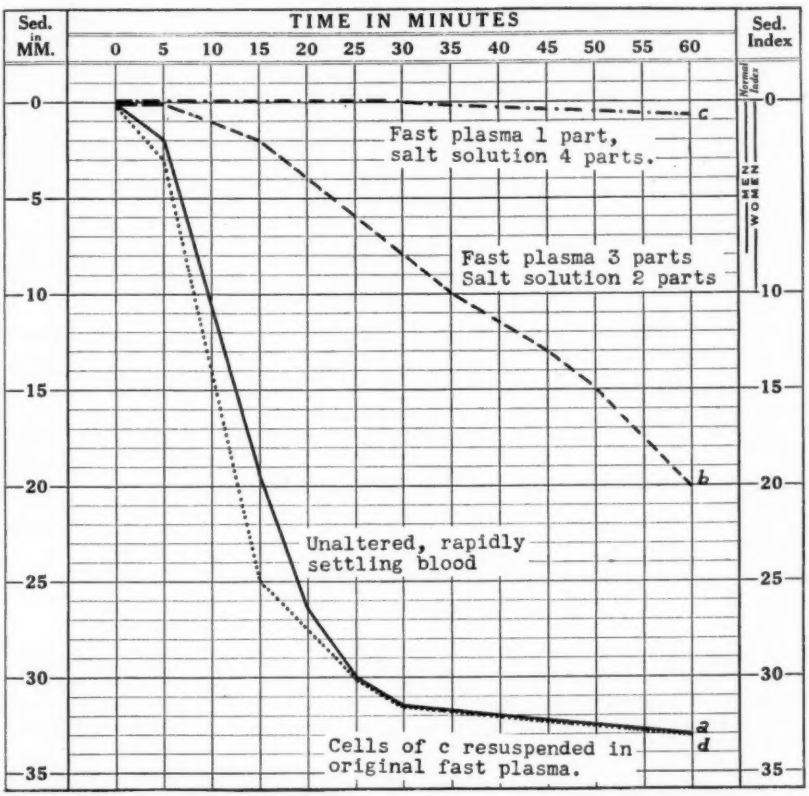

FIG. 4.—Experiment II. Addition of physiologic salt solution to rapidly settling blood.

As in the previous experiment, the difference in behavior of the red cells lies in their ability to form aggregates. In plasma diluted with saline, they fail to form rouleaux. In "fast" plasma they form rouleaux readily. The number of cells in suspension remained the same throughout the experiment. Other details are omitted to conserve space.

Experiment III. *Red cells of rapidly sedimenting blood suspended in Ringer's solution and then resuspended in "fast plasma."* Results with Ringer's solution are identical with those obtained in physiologic salt solution.

Experiment IV. *Addition of lecithin to rapidly settling blood.* When lecithin (1 mg. to 1 cc. of blood) was added to rapidly sedimenting blood, the red cells which previously settled rapidly (Fig. 5 *a*) failed to sediment but remained in suspension indefinitely (Fig. 5 *b*). When the lecithin-treated cells were carefully washed with saline and resuspended in "fast" plasma they again settled rapidly (Fig. 5 *c*).

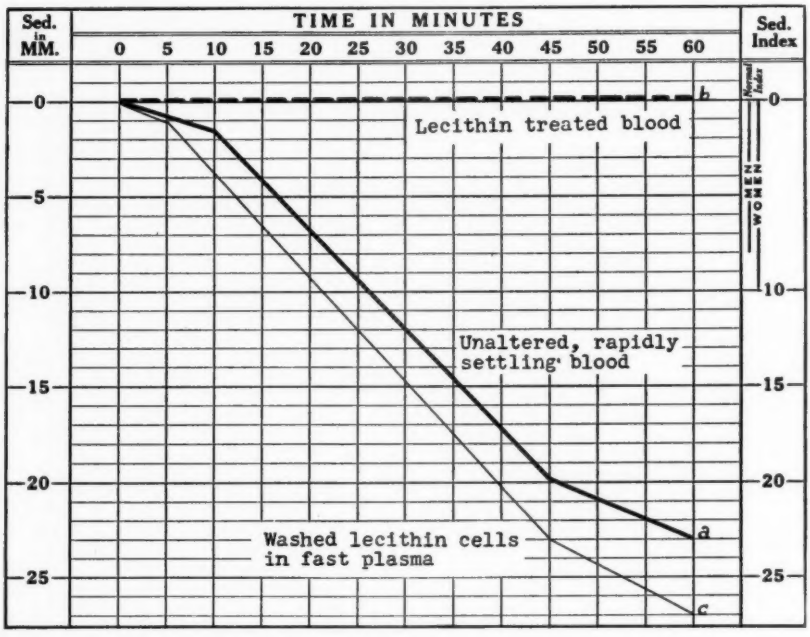

FIG. 5.—Experiment IV. Addition of lecithin to fast settling blood.

In the presence of lecithin the cells failed to form rouleaux, but regained that power in "fast" plasma. An interesting observation in the lecithin-treated cells was the inflated appearance of the red cells, even after repeated washing with saline. The aggregates of the latter consisted of fewer cells, but each aggregate appeared to weigh approximately the same as the aggregates with more cells of the original sample of rapidly settling blood, hence the rate of sedimentation was approximately the same. The percentage of cells engaged in rouleaux formation was the same in both samples of blood. This observation furnishes additional support to the statement that the rapidity of settling is independent of the size or shape of the individual cell, but depends on the total *mass* of the formed aggregate.

The following table lists the average and the maximum number of cells per aggregate and the percentage of cells engaged in rouleaux formation.

	Average No. of cells per aggregate.	Maximum No. of cells per aggregate.	% of cells engaged in rouleaux formation.
Graph A (unaltered, fast settling blood)	20	40	9
Graph B (lecithin treated blood)	No rouleaux formation		
Graph C (washed lecithin cells in fast plasma)	5	22	85

Experiments V, VI, and VII. *Addition of sodium oleate, bile salts or formaldehyde.* When sodium oleate, bile salts or formaldehyde was added to rapidly settling blood, sedimentation was practically inhibited and results were identical with those obtained with lecithin.

Experiment VIII. *Addition of acacia to slowly settling blood.* When acacia was added to slowly settling blood, the erythrocytes which previously settled slowly (Fig. 6 *a*) then settled rapidly. As more acacia was added the rate of settling was increased proportionately (Fig. 6 *b*, acacia, 1 part; blood, 9 parts; Fig. 6 *c*, acacia, 1 part; blood, 4 parts). When the acacia-treated cells were washed in saline and resuspended in "slow" plasma they again sedimented slowly, although not as slowly as the unaltered cells

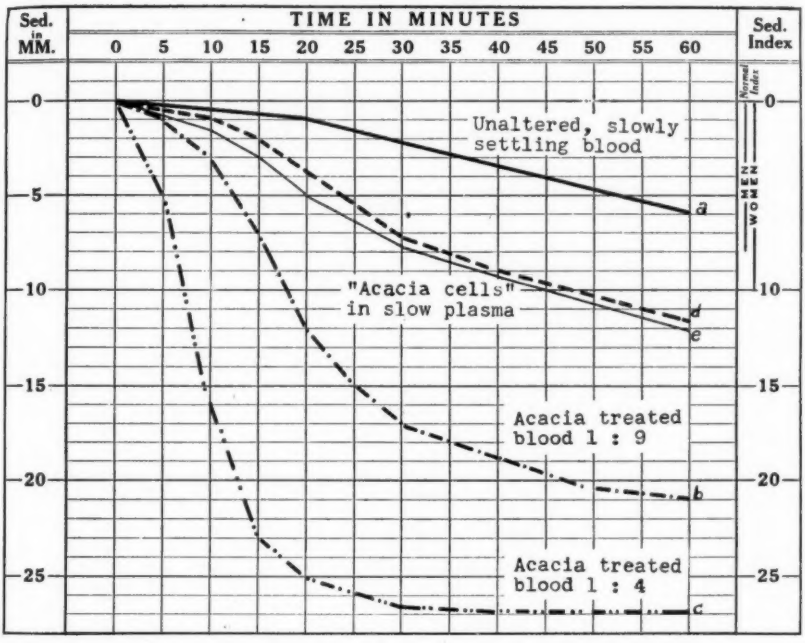

FIG. 6.—Experiment VIII. Addition of acacia to slowly settling blood.

(Fig. 6 *d* and *e*). The rapidity of settling of red cells is intimately bound up with their ability to form rouleaux.

The following table lists the average and the maximum number of cells per rouleaux, and the percentage of the cells engaged in rouleaux formation under the different conditions of experiment.

	Average No. of cells per aggregate.	Maximum No. of cells per aggregate.	% of cells engaged in rouleaux formation.
Graph A (unaltered, slow settling blood) .	2	3	5
Graph B (acacia-treated blood 1:9) . .	15	40	70
Graph C (acacia-treated blood 1:4) . .	30	90	95
Graph D (acacia cells in slow plasma) . .	3	6	30
Graph E (acacia cells in slow plasma) . .	3	6	30

Experiments IX, X, and XI. *Addition of agar, casein or gelatin to slowly settling blood.* When one of the above hydrocolloids was added to slowly settling blood, sedimentation was increased and the results were similar to those obtained with acacia.

Experiments XII and XIII. *Sedimentation in defibrinated blood and in plasma after heat coagulation.* Sedimentation of red cells continued fast in defibrinated plasma of rapidly settling blood (Fig. 7 *c*) and in the plasma of rapidly settling blood from which fibrinogen had been removed by heat coagulation (Fig. 7 *b*). The tendency to rouleaux formation was only slightly interfered with. Figure 7*a* is the unaltered fast-settling blood.

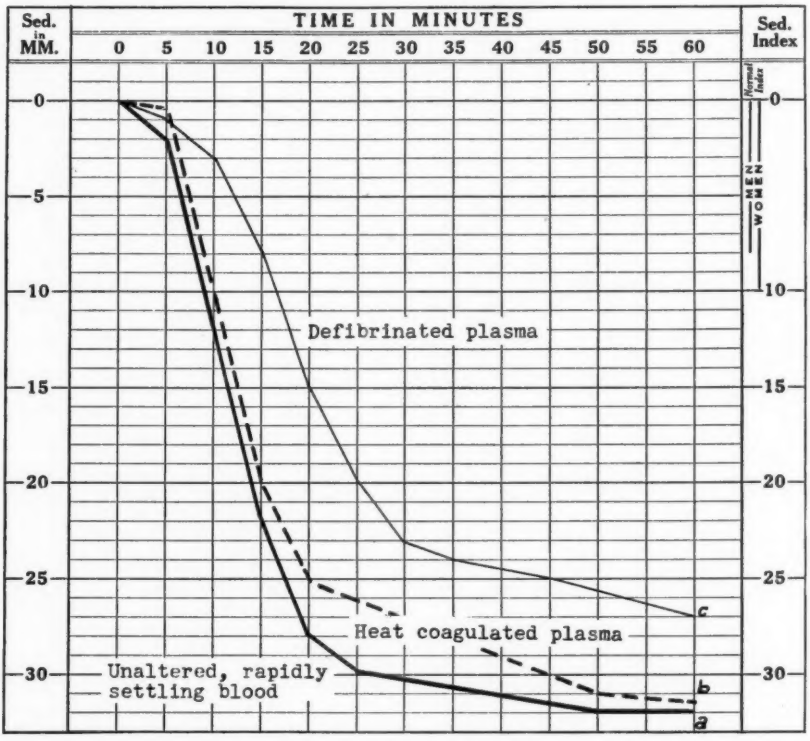

FIG. 7.—Experiments XII and XIII. Sedimentation in defibrinated blood and in plasma after heat coagulation.

The following table lists the average number and the maximum number of cells per aggregate, and the percentage of cells engaged in rouleaux formation.

	Average No. of cells per aggregate.	Maximum No. of cells per aggregate.	% of cells engaged in rouleaux formation.
Graph A (unaltered, fast settling blood)	25	60	98
Graph B (heat coagulated plasma)	25	60	98
Graph C (defibrinated plasma)	15	40	85

Experiment XIV. *Influence of time on rapidity of blood sedimentation.* It is well known that the sedimentation phenomenon disappears with time when blood is permitted to stand at room temperature. Cells which previously settled rapidly will in time refuse to settle. When the red cells which did not sediment were resuspended in fast plasma, they again settled rapidly. Rapidity of sedimentation was once again intimately bound up with rouleaux formation. Details are omitted to conserve space.

Experiment XV. *Relationship of rouleaux formation to sedimentation velocity and of rouleaux formation to red cell count.* Blood sedimentation determinations were made on 104 individuals, for the most part unselected hospital patients. The sedimentation velocity (drop in millimeters per unit of time) was determined for each blood sample by noting on the sedimentation graph the highest number of millimeter drop in any 5-minute interval during the first hour and expressing the result in millimeters.

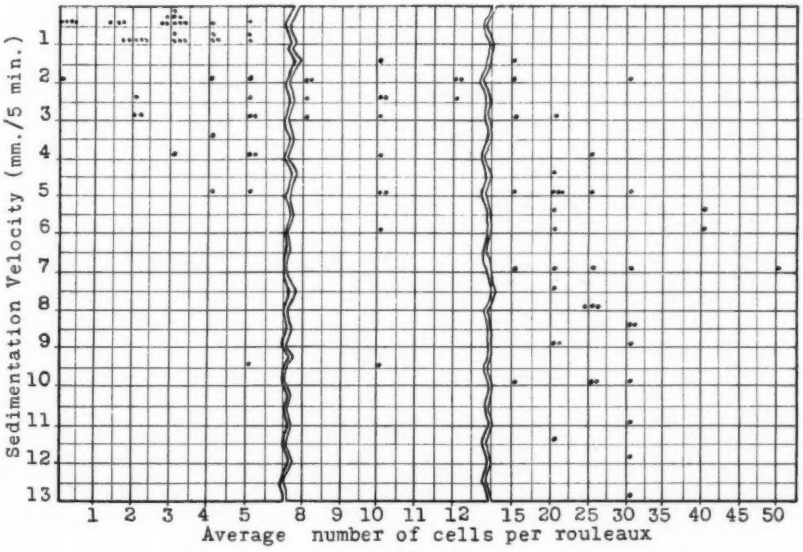

FIG. 8.—Experiment XV. Sedimentation velocity and size of rouleaux.

Rouleaux formation was studied carefully in each patient. Three determinations were made: (1) the average number of cells per aggregate; (2) the highest number of cells per aggregate; and (3) the percentage of cells engaged in rouleaux formation. Red cell counts were made on 91 of the 104 blood samples. The sedimentation velocity, or the maximum number of millimeters the upper level of the sedimenting column of red cells settled in any 5-minute period during the first hour, was plotted against the average number of cells per rouleaux and the corresponding red cell count, and graphs were constructed.

The graph in Figure 8 indicates a close parallelism between sedimentation velocity and the tendency to rouleaux formation. There are few discrepancies at either extreme and these, in part at least, can be explained on technical grounds. Slow sedimentation is invariably associated with small size aggregates and *vice versa*. It is fair to assume that the parallelism would be more striking had a less crude method been used for determining

the mass of the aggregate than that of counting the number of cells per aggregate in a few microscopic fields. From the experiment with lecithin (Experiment IV) we are convinced that the size of the red cells is a determining factor in making up the mass of the aggregate, and the larger the cells the fewer the cells per aggregate and *vice versa*. It is also apparent that the procedure of diluting the sample of blood with saline to facilitate the study of aggregation has inherent objections and limitations and involves considerable of a personal equation.

When sedimentation velocity is compared with the red cell count, the relationship is not nearly as close (Fig. 9). Although faster sedimentation velocities are more apt to be accompanied with anemia, it must be remembered that in the cases where sedimentation is rapid, there is usually an associated secondary anemia, the result of the underlying disease, such as advanced cancer, independent of alterations in the suspension stability of the blood.

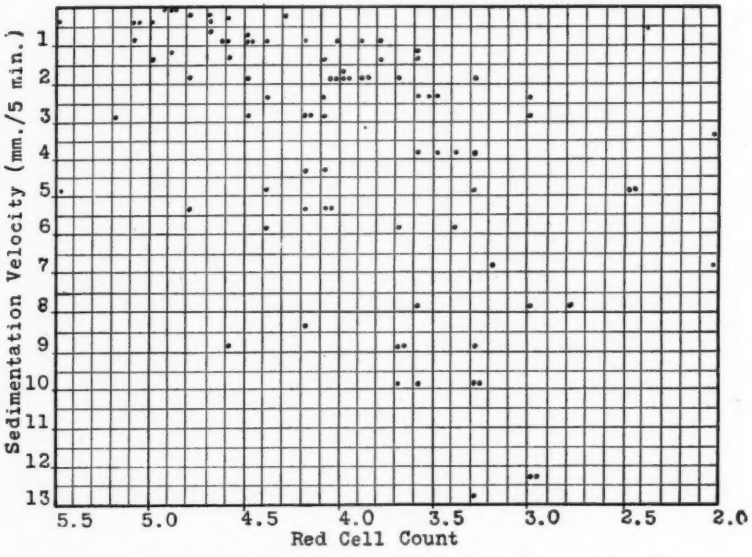

FIG. 9.—Experiment XV. Sedimentation velocity and red cell count.

It is certainly true that sedimentation velocity can be slow or fast and the cell count remain practically the same. Thus a sedimentation velocity of 1 mm. per 5 minutes can be obtained with a red cell count of 5,500,000 as well as with a count of 2,400,000 or any intermediate figure.

Blood Sedimentation and Stokes' Law of Hydrodynamics. The observation that it is the size of the aggregate and not the number of unengaged cells in suspension that is responsible for rapid sedimentation, fits in more or less with Stokes' law of hydrodynamics, which is concerned with sphericle particles held in suspension in a fluid of less specific gravity than the particle itself. According to this law, the rate of settling is proportional to the difference between

the specific gravity of the particle and that of the fluid, inversely proportional to the viscosity of the fluid and directly proportional to the square of the radius of the suspended particles.

Differences between the specific gravity of the red blood cells and that of the plasma are without significance. Nor does the viscosity of the blood have an important bearing. The important factor is the size of the particle in suspension.

In this instance, the size of the particle does not refer to the individual cell, but to the size of the *aggregate*. The larger the aggregate, the more rapid the settling and *vice versa*. The establishment of this fact explains such an apparent paradox as increased sedimentation and increased blood viscosity when the reverse would be expected to hold true; and slow sedimentation in the presence of anemia. The individual red cell, regardless of its size or shape or hemoglobin content, has so little mass and the resistance it must overcome is so considerable that it sediments very slowly. On the other hand, when aggregates are formed, the mass of the individual aggregates becomes sufficiently great that they more easily overcome the viscosity of the plasma and settle rapidly. This explains the little increase in sedimentation found in the presence of marked anemia provided there is no associated pathologic condition which in itself may produce rapid sedimentation.

The Three Phases of Blood Sedimentation. We are now in a position to study in detail blood sedimentation as recorded in the form of graphs. Cutler has recognized four distinct graphs, a horizontal line, a diagonal line, a diagonal curve and a vertical curve. The horizontal line is normal and denotes slow sedimentation. The other graphs are abnormal findings and indicate various degrees of increased sedimentation. The vertical curve which indicates the most rapid form of sedimentation, consists of three phases. The first is a slow phase, during which the cells are grouping themselves and forming aggregates. This aggregation period usually varies from 5 to 15 minutes, occasionally as long as 30 minutes. Once formed, the aggregates fall uniformly, more or less in accordance with Stokes' law. This is the second or settling phase and gives rise to the sedimentation phenomenon.

The aggregates settle at their respective speeds indefinitely, depending on the length of the tube until they reach bottom. The aggregates that follow pack on top and the packing stage, or third phase, of sedimentation sets in. This phase is always slow. When all aggregates have settled tightly, sedimentation comes to a standstill.

It is apparent that by the time packing ensues, the sedimentation phenomenon has already taken place and that the packing of cells represents only a rough hematocrit finding, recording the space in the tube occupied by the cells. The packing stage is the only phase

of sedimentation that is materially influenced by the degree of anemia. The fewer the cells, the less volume they occupy.

The three phases, aggregation, sedimentation and packing are found in all graphs, in the horizontal normal as well as in the definitely abnormal vertical curve. The difference is in the time required to complete the second stage, or stage of sedimentation which depends on the mass of the aggregates formed during the first or aggregation phase, which in turn is a function of the plasma.

To study the sedimentation phenomenon, one should be concerned principally with the second phase, or phase of settling. The common practice has been, however, to determine the distance the cells have settled at the end of an arbitrary time interval, such as 1 hour, and to express this as the blood sedimentation rate. When sedimentation is rapid and the packing phase has been reached in less than 1 hour, the finding at the end of an hour must reflect not only the sedimentation velocity of the aggregates, but also cell volume, and hence be influenced by the degree of anemia present.

The complete sedimentation graph is therefore seen to reflect two things, blood sedimentation and anemia. The two, however, occupy different positions on the graph and are readily distinguishable. The first two phases of the graph represent the grouping of erythrocytes into aggregates and their sedimentation and are the result of factors within the plasma. The number, size, or shape of cells has little to do with either phenomenon. On the other hand, the third or packing phase records cell volume and is necessarily influenced by such factors as size, shape and number of cells.

The Fallacy of Correcting for Anemia. It is the obvious reflection of the anemia in the packing phase and in the sedimentation index, when sedimentation is rapid and complete within the hour, that has led to efforts to correct for anemia. The proponents for correction for anemia point out, and rightly so, that whenever cell volume is normal, the sedimentation index, that is, the total drop at the end of 1 hour expressed in millimeters, is less than when anemia is present. The decreased sedimentation index after correction, would in their opinion represent blood sedimentation with the anemia factor eliminated. The false premise of this supposition is apparent. Volume percentage and blood sedimentation, as previously explained, are two different things and for all practical purposes have little in common. The confusion results from using a single arbitrary reading as a measure of sedimentation velocity at a time when the sedimentation phenomenon is well advanced.

In the course of our study we corrected a considerable number of blood samples for anemia and plotted sedimentation graphs on the uncorrected as well as on the corrected blood. In a number of instances we corrected the same sample both by volume and by cell count. In every case, when plasma was removed, sedimentation became slower and in direct proportion to the quantity of plasma

removed. We next studied the effect of the removal of plasma on the size of the red cell aggregate and it soon became apparent that the removal of plasma interfered with the mechanism of rouleaux formation and resulted in smaller aggregates of red cells.

It thus became clear that it was the reduction in the size of the red cell aggregate and not the greater number of cells in suspension, as is commonly believed, that was responsible for the slower sedimentation rate that invariably followed the removal of plasma to correct for anemia.

When a relatively small quantity of plasma was removed, the mechanism of sedimentation was little interfered with. Although sedimentation was slower in the corrected sample, the shape of the graph was not altered. The corrected curve showed the same general characteristics of the uncorrected curve, only at a slower rate.

On the other hand, when a large quantity of plasma was removed, as was the case when anemia was considerable, 3,000,000 or less, the mechanism of aggregation was seriously interfered with and sedimentation became extremely slow even though the patient from whom the blood was taken was quite ill (Fig. 10).

The proponents for correction call this "over-correction," although the blood count of the corrected sample was 5,000,000, as in other corrected blood samples. This observation is not over-correction. It is a deliberate interference with the mechanism of aggregation of red cells to the point where the sedimentation phenomenon practically disappears.

It is impossible to devise a formula for correction for anemia, based on keeping constant the percentage relationship of cell volume or cell count to plasma volume before instituting sedimentation readings, for the simple reason that the factors responsible for the aggregation of red cells, and hence increased sedimentation, which reside in the plasma, are extremely potent and their concentration specific for the different plasmas. It is the variability of the concentration of these factors in the plasma that determines sedimentation rate and not the quantity of plasma or the number of cells in suspension.

It is not surprising, therefore, to find that those laboratories employing "correction" may report from time to time normal sedimentation findings which do not at all check with the clinical state of the patient.

Artificial Anemia and Sedimentation Velocity. Another observation cited as justification for correction is that the rapidity of settling of red cells can be increased in normal and pathologic blood by simply removing cells and producing an artificial anemia. The natural assumption has been that the increased sedimentation results from a simple reduction in the number of cells in suspension.

Experiment XVI clearly shows that this assumption is not justified. When the proportion of plasma is artificially increased by

the removal of cells, the activating factors in the plasma responsible for rouleaux formation have a greater opportunity to drive the remaining cells into rouleaux. The aggregates in slowly settling plasma, however, are never large even when the number of red cells are reduced to 1,000,000 or less. This explains the absence of the steepness to the curve so characteristic of rapidly settling blood, the result of disease with or without an associated secondary anemia. No vertical curves appear because there are no large aggregates (Fig. 11).

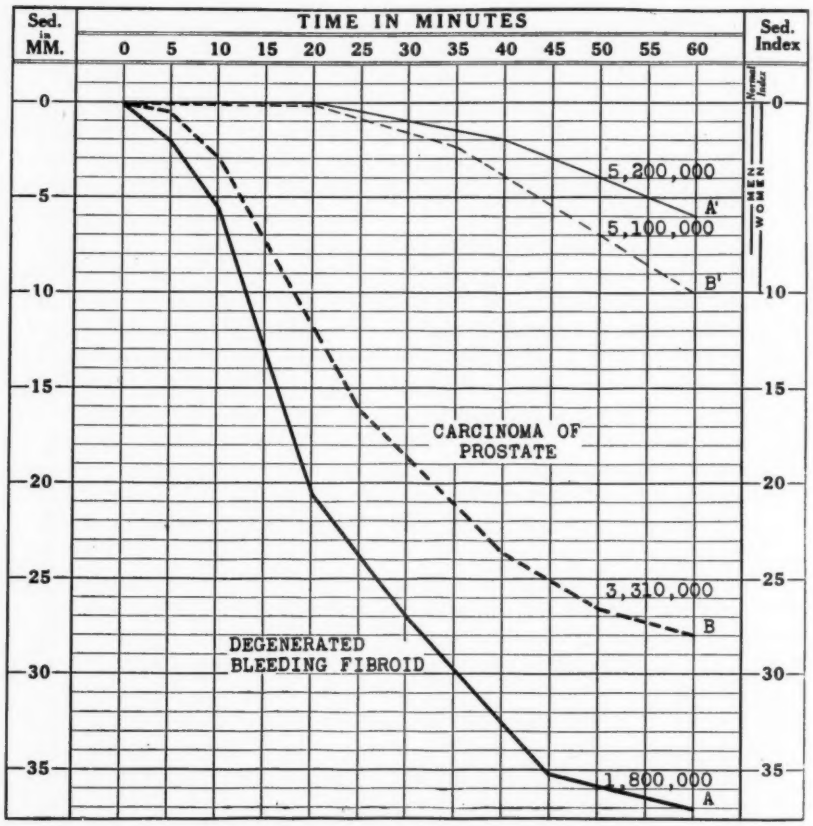

FIG. 10.—Misleading sedimentation rate after "correction."

That the rapid sedimentation is not the result of simply reducing the number of erythrocytes can be further established by suspending the same cells and the same number of cells in physiologic salt solution where there is no tendency to rouleaux formation. Sedimentation becomes extremely slow even though the anemia be marked (Fig. 12).

A dilution experiment, however, fails to make clear the clinical observation that marked anemia, when not associated with a disease which in itself may cause rapid sedimentation, does not result in any significant increase in blood sedimentation. The explanation

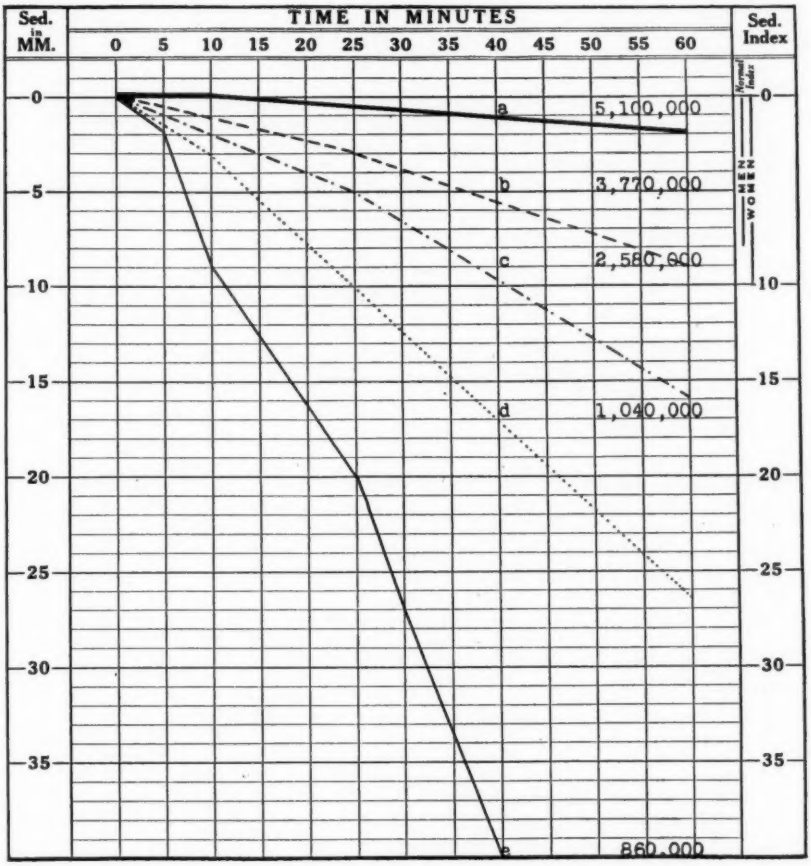

FIG. 11.—Experiment XVI. Artificial anemia and blood sedimentation.

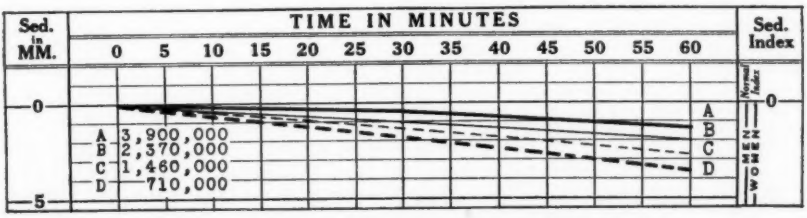

FIG. 12.—Experiment XVI. Artificial anemia in saline.

probably is that the dilution experiment involves large scale manipulations on a relatively small quantity of blood, a phenomenon which does not take place during life.

Experiment XVI. *Artificial anemia and blood sedimentation.* The rapidity of blood sedimentation and the red cell counts of 10 healthy individuals were determined. Each blood sample was next diluted by the addition of the patient's own plasma to contain approximately 4, 3, 2, and 1 million red cells per c.mm. and the rapidity of blood sedimentation determined for each dilution.

All graphs were found to be straight lines, no matter how marked the anemia, and the corresponding aggregates to consist of relatively few red cells. The largest aggregates observed were about 18 cells per rouleaux with counts of 1,000,000 or less.

The following table lists the average number of cells, the maximum number of cells and the percentage of cells engaged in rouleaux formation in the case, the sedimentation graphs of which are plotted in Figure 11.

	Average No. of cells per aggregate.	Maximum No. of cells per aggregate.	% of cells engaged in rouleaux formation.
Graph *a* (5,100,000 r.b.c.)	2	2	25
Graph *b* (3,770,000 r.b.c.)	3	6	25
Graph *c* (2,580,000 r.b.c.)	7	15	50
Graph *d* (1,040,000 r.b.c.)	5	16	75
Graph *e* (860,000 r.b.c.)	5	18	85

No close relationship existed between the degree of artificial anemia and sedimentation index. Each sample of blood appeared to have its own sedimentation characteristics, which it retained throughout the dilution experiment, and graphs with widely divergent sedimentation indices were obtained with practically identical blood counts.

The following table lists the sedimentation index obtained with each of the 10 healthy blood samples, when the red cells in suspension were reduced artificially by the addition of the patient's own plasma to approximate 2,000,000. The sedimentation indices with other dilutions are not recorded, to conserve space.

Case.	Original sedimentation index.	Original blood count in millions.	Artificial anemia (r.b.c. count nearest 2.0 million).	Corresponding sedimentation index.
1	1.5	4.9	2.2	18.5
2	2.0	4.7	2.2	17.0
3	2.0	5.2	1.9	16.0
4	2.0	4.6	2.1	9.0
5	2.5	5.1	2.2	26.0
6	2.5	4.6	2.0	27.5
7	4.2	3.9	2.4	20.5
8	4.5	4.4	2.3	19.5
9	5.5	4.7	2.1	33.0
10	9.5	4.6	2.4	25.0

When the red cells were separated from their plasma medium and resuspended in saline of equal percentage volume and sedimentation graphs constructed, sedimentation was always slow and the graph always a horizontal line, regardless of the number of cells in suspension (Fig. 12). The ability of the red cells to form aggregates was completely lost and microscopically the cells appeared as well formed disks entirely unengaged.

Clinical Observations. Further proof that anemia plays a minor rôle in the rapidity of blood sedimentation is found in the following clinical observations.

A. When pronounced anemia is associated with a disease which in itself is not distinguished by an increased sedimentation rate, such as sickle-cell anemia or bleeding duodenal ulcer, sedimentation of erythrocytes is always slow. Figure 13 *b*, *e*, illustrates sedimentation graphs in sickle-cell anemia and in bleeding duodenal ulcer with anemia of 2,500,000 and 1,360,000 respectively. In spite of the decided anemia, sedimentation is increased little beyond normal.

B. When severe anemia is associated with a disease which in itself may produce a moderate increase in sedimentation, the sedimentation index will be high depending on the degree of anemia present, but the graph will have only a slight curve. A good example is bleeding fibromyoma of the uterus which has undergone mild degeneration (Fig. 13*k*). Anemia in which the counts are higher than 3,500,000 are without appreciable significance.

C. When marked anemia is associated with a disease which in itself may produce rapid sedimentation, such as advanced, ulcerating cancer, the sedimentation index will be high, but there will also be an unquestioned steepness to the graph (Fig. 13, Graph *l*). The steepness of the graph reflects disease; the index portrays anemia as well.

It is obvious from a study of Figure 13*a*, which portrays sedimentation graphs obtained in various clinical conditions, a list of which follows, that the concentration of red cells may vary greatly for the same type of curve and for the same sedimentation index.

Blood sedimentation and anemia are independent phenomena and have little in common.

Conclusions. The present study is a critical appraisal of the scientific basis for the theory that anemia plays an important rôle in the sedimentation of erythrocytes. Consequently, the justification for current efforts to correct for anemia is considered. Our study leads us to the following conclusions:

1. Anemia has little to do with the phenomenon of blood sedimentation. Rapid settling is the result of the red cells forming large aggregates or rouleaux. If no aggregation takes place, sedimentation is slow no matter how marked the anemia.

2. The ability of the red cells to form aggregates is a function of the plasma and is specific for that plasma. The specificity is little influenced by the size, shape or number of cells in suspension.

3. Once aggregates form, they settle at a given rate of speed more or less in accordance with Stokes' law of hydrodynamics. The greater the mass of the aggregate, the more rapid does settling take place and *vice versa*.

4. The current practice of letting a single determination at the end of an arbitrary time interval, such as 1 hour, express blood

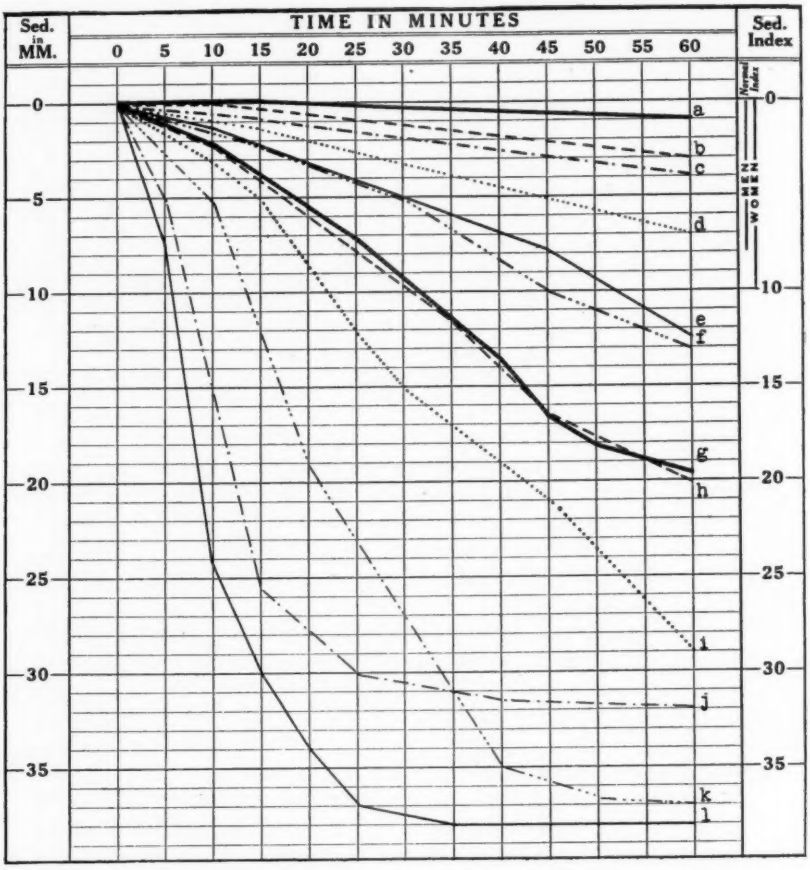

FIG. 13.—Sedimentation graphs and indices in various clinical conditions.

FIG. 13*a*.—SEDIMENTATION INDEX AND ANEMIA.

	Sedimentation Index.	R.b.c.
a. Healthy male	1	5,100,000
b. Sickle-cell anemia	2	2,550,000
c. Secondary anemia	3	3,860,000
d. Healthy male	7	4,090,000
e. Bleeding peptic ulcer	12.5	1,360,000
f. Coronary disease	13	3,090,000
g. Primary pernicious anemia	19.5	2,320,000
h. Postoperative (nephropexy)	20	5,220,000
i. Carcinoma of stomach	29	2,180,000
j. Lobar pneumonia	32	4,000,000
k. Degenerated bleeding fibroid	37	1,860,000
l. Carcinoma of lung	38	2,400,000

sedimentation fails to study critically the sedimentation phenomenon and leads to erroneous conclusions.

5. When multiple readings are employed, the nature of the graph isolates the anemia factor (packing phase) from blood sedimentation (aggregation and sedimentation phases). The shape of the curve portrays disease, the index reflects anemia as well.

6. One cannot correct for anemia and still get consistent sedimentation findings. The very removal of plasma in an endeavor to correct for anemia interferes with the mechanism of rouleaux formation and sedimentation becomes slow in proportion to the amount of plasma removed.

7. When considerable plasma is removed, the laboratory may report normal sedimentation findings which do not check at all with the clinical state of the patient, a phenomenon referred to in the literature as "over-correction."

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NORMAL VENOUS PRESSURE AS DETERMINED BY A DIRECT METHOD.

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Normal values for venous pressure as given in the literature cover the wide range of 30 mm. to 150 mm. of water. Bedford and Wright,[1] for instance, have quoted figures for the limits of normal determined by direct methods as follows: Castellotti 40 to 70 mm. of water, Corradi 80 to 130, Villaret 120 to 130, Gazzotti 130 to 140. Evans[4] has collected the following figures for the upper limits of normal, also obtained by direct methods: Schott 130 mm. of water, Moog and Ehrmann 100, Arnoldi 103, Fuchs 125, Blumgart 100, Taylor 100, Von Gonczy 120, Ernst and Stagelschmidt 120. Since all the

above determinations were made on "normal subjects," it is probable that the differences obtained resulted from differences in technique.

Further data from the literature may be tabulated as follows:

Author.	Date.	Direct method.	Subjects studied.	Venous pressures.	
				Extremes.	Average.
Bedford and Wright[1]	1924	Claude	34 medical students	90% were between 50–150 mm. of water	Not given
Evans[4b]	1932	His own	Miscellaneous group having various diseases	75–175 mm. of water	Not given
				Majority between 100–150	
Leaman[8]	1935	Evans	Normal group	40–120 mm. of water	Not given
Wartman[10]	1935	Griffith, Chamberlain, and Kitchell	31 normal persons	60–120 mm. of saline	83 mm.
Harrison[7]	1936	Moritz and Tabora	20 normal persons	30–75 mm. of saline	54 mm.
Berger[2]	1937	Moritz and Tabora	20 normal persons	Not given	77 mm. of 5% sodium citrate solution
Gibson and Evans[5]	1937	Evans[4a]	90 normal persons	50–120 mm. of water	80 mm.

Moritz and Tabora[9] described their direct method in 1910. Accurate details of the position of the subject's shoulders and arm were given, and photographs of their apparatus in use were included. They studied 29 "normal subjects," obtaining an average venous pressure reading of 52 mm. of physiologic saline, with the majority falling between 40 to 80 mm.

In 1934, Griffith, Chamberlain, and Kitchell presented their modification of the method of Moritz and Tabora. Besides a marked simplification of the apparatus, these workers also changed the technique of its use. Thus instead of maintaining the arm in right angle abduction at the shoulder, with slight flexion at the elbow, and with the hand in half pronation, they prescribed that the "arm and forearm (be) extended by the side in supination." From 250 readings on normal subjects they gave an average range of from 80 to 110 mm. of physiologic saline, with a normal range of 60 to 120 mm.

The purposes of the study presented below were to discover, if possible, an explanation for the difference between the figures of Moritz and Tabora and those of Griffith, Chamberlain, and Kitchell; to establish a standard technique for the method of the latter; and to determine thereby normal venous pressure values.

Method. The apparatus was constructed according to the specifications of Griffith, *et al.* The theory of its use may be stated briefly. By means of a level fitted with accurately measured legs and clamps for a glass tube, the zero point of a manometer can be held at the level of the right auricle. A saline column in the manometer is carried into a vein of the subject's arm by means of rubber tubing, a Kaufman-Luer side arm syringe and an intravenous needle. Within certain limits, the system thereby created may be considered a direct tube-and-fluid connection between the venous entrance to the right auricle and the manometer. Thus any pressure effect at the former will be reflected at the latter.

TABLE 1.—VENOUS BLOOD PRESSURE IN NORMAL SUBJECTS (GRIFFITH POSITION).

Case.	Age.	Sex.	Venous pressure (mm. of saline). Right arm.	Left arm.	Average.
1	23	F	85	95	
			120	120	
			105	105	105
2	22	F	...	100	
			115	135	
			120	120	118
3	25	M	110	(150)	
			105	(140)	
			(140)	(180)	
			115	115	111
4	23	M	130		
			125		
			125	130	127
5	28	M	130		
			110	...	120
6	23	M	100		
			130	125	
			95	105	111
7	23	M	95		
			85		
			105	105	
			60	60	85
8	24	M	75		
			90		
			90	105	90
9	24	M	(150)	100	
			105	105	
			115		
			115	95	106
10	25	F	80		
			100	...	90
11	23	M	140	140	140
12	22	M	130	110	120
13	32	F	110	110	110
14	23	M	(180)		
			(175)		
			(145)	(130)	
			(180)	(140)	
15	24	M	(180)		
			(190)		
			(255)	(125)	

The first series of tests were made on a group of 14 medical students and one nurse, all of whom were perfectly healthy. The Griffith technique was used, including the feature of extending the arm and forearm by the side in supination. The results of these tests are given in Table 1. An average of 4 determinations was obtained on each subject.

Of the 65 readings recorded, the 15 appearing in parentheses were thought to be inaccurate either because they failed to agree with other readings made on the same subject, as in Case 9, or because the behavior of the fluid level during the experiment was such that no definite value could be assigned. At times the fall in the saline column after removing the reservoir was unduly slow, or perhaps when a level seemed accurately attained, a moderate inhalation

would reduce it by 20 to 30 mm. to a new level. Occasionally paradoxical respiratory fluctuations were encountered in which the venous pressure rose with inspiration and fell with expiration. Under these various circumstances, the readings were considered without value.

Among the 50 supposedly reliable determinations, there were high and low extremes of 140 mm. and 60 mm. of physiologic saline solution. The average value for venous pressure of the first 13 cases was 110 mm. The results obtained on the next 2 cases (14 and 15) were not only far higher but were also poorly defined. Furthermore, the average of 110 mm. was known to be twice as high as the average described by Moritz and Tabora. Therefore, it was suspected that all the readings were unduly high and that the technique was at fault.

TABLE 2.—NORMAL VENOUS BLOOD PRESSURE (MORITZ AND VON TABORA POSITION).

Case.	Age.	Sex.	Venous pressure. (mm. of saline). Right arm.	Left arm.	Average.
14	23	M	75	75	
			90	100	
			75	80	82.5
15	24	M	75	65	70
16	24	M	85	85	
			90	85	86
17	24	M	35	35	
			30	30	32.5
18	24	M	95	95	
			80	80	87.5
19	23	M	85	85	
			85	80	84
20	22	M	95	95	
			75	85	87.5
21	24	M	85	95	
			90	90	90
22	24	M	90	90	
			80	80	85
23	24	M	85	90	
			55	65	
			55	75	71
24	24	M	75	75	
			65	75	72.5
25	25	M	95	90	
			100	95	95
26	29	M	55	55	55
27	22	M	50	50	50
28	22	M	90	85	
			100	95	92.5
29	22	M	70	70	
			65	65	67.5
30	22	M	75	80	
			80	80	79

Cases 14 and 15 were again studied in exactly the same manner excepting that the position of the arm was maintained according to the instructions of Moritz and Tabora. The results were strikingly different. The levels were obtained quickly, and the figures were found to be much lower (see Table 2). During each of these 8 tests,

when the end point had been established, the arm was carefully shifted to the position previously used. Invariably the level promptly rose. For instance, in the right arm test of Case 15 the pressure rose within 45 seconds from 75 mm. to 200 mm. Both of these men had particularly large upper arms with firm flesh. Thus the obvious explanation for the phenomena described would seem to be that on adduction of the arm, squeezing of the veins occurred about the shoulder and axilla, thereby raising the venous pressure at the elbow. Similar shifts in position of the arm were studied on 15 other subjects. Without fail adduction caused a rise in pressure; and abduction, a fall. It was observed that the thinner the arm and the flabbier the musculature and fat layers, the less was the pressure excursion. This fact is considered supporting evidence for the above explanation. In view of these findings, all subsequent determinations were done with the test arm in at least 70 degree abduction at the shoulder.

Another possible explanation for venous pressure irregularities attending changes in the position of the test arm was offered in 1931 by Brandt and Katz.[3] They believed that adduction of the arm affected the anatomic relationship between the clavicle, first rib, and subclavian vein in such a way as to exert pressure on the vein. They found that paradoxical respiratory changes and unduly high venous pressures could be abolished by placing the arm in the position advocated by Moritz and Tabora.

The Technique Used in Obtaining the Figures Recorded in Tables 2 and 3. The subject is requested to remove all clothing encircling the upper arms and shoulders or covering the angle of Louis. He then reclines on his back on a perfectly flat, firmly cushioned examining table. A thin pillow under the head is permissible. A blood-pressure cuff is adjusted to the upper arm. The lower arm is supported on a small adjoining table, using folded towels to rest it in the most comfortable position (Fig. 1). This maneuver nearly always brings the antecubital surface to lie close to the horizontal level of the posterior axillary line. The subject lies close enough to the edge of the examining table so that his upper arm is suspended free from any points of contact with either table. He is then instructed to breathe at the rate of about 12 respirations per minute. A metronome has proved useful in this respect. If it is set at 48 strokes per minute, the subject inhales slowly for 2 beats and exhales for 2 beats. Under the above conditions, he rests for 15 minutes.

Meanwhile, the entire apparatus, excepting the wooden leveling device, is sterilized by boiling. When all is assembled, about 12 to 15 cc. of sterile physiologic saline are poured into the reservoir. The fluid is allowed to flow through the system until all bubbles have been eliminated and the stream is seen to flow briskly and evenly. This usually takes about 4 to 5 cc., leaving the 8 to 10 cc. necessary for the test.

When the 15 minutes have passed, the pulse and arterial blood pressure are taken. The antecubital space is then cleansed with alcohol. The cuff is inflated to a pressure half way between the diastolic and systolic readings, and the needle is promptly introduced preferably into the median basilic vein. As the blood enters the syringe, the cuff is quickly deflated and removed from the arm. At the same time, the assistant is raising the manometer and reservoir as high as possible, to insure a maximum head of pressure of the saline column which is allowed to wash the blood out of the syringe into the vein. During the $\frac{1}{2}$ to $\frac{3}{4}$ minute it takes adequately to clear the syringe, the arm is adjusted comfortably with abduction

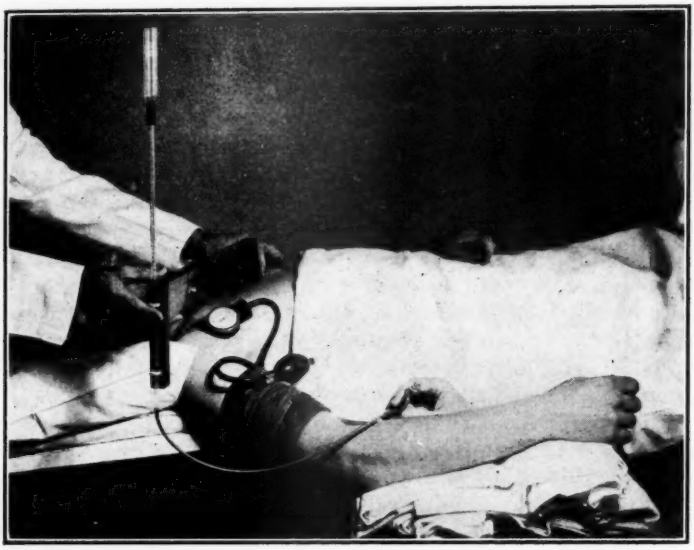

FIG. 1.—The apparatus as described by Griffith, Chamberlain, and Kitchell, and the position of the arm as prescribed by Moritz and Tabora.

at the shoulder to approximately a 70-degree angle. The elbow is slightly flexed and the forearm is rested in half pronation (Fig. 1). The position of the needle in the vein may then be altered to insure the fastest flow of saline. This can be determined by observing the falling fluid level in the reservoir.

When the speed of flow is maximum and the syringe is practically clear, the shorter leg of the level is set at the angle of Louis. The reservoir is removed by simply sliding it off from the manometer. The excess saline is allowed to spill, since any attempt to pinch the rubber connection is apt to introduce a bubble into the manometer.

As the reservoir is detached, the position of the second hand of a watch is noted. The fluid level normally falls in the manometer at the following rate in millimeters per successive 5 seconds:

The first 5 secs.	100 mm.	The first 5 secs.	20 mm.
5 secs.	50 mm.	5 secs.	10 mm.
5 secs.	40 mm.	5 secs.	5–10 mm.
5 secs.	30 mm	5 secs.	5–10 mm.

As the venous pressure level is approached, the meniscus is often seen to descend in step-like fashion with sharp falls on inspiration and stationary levels or possibly slight rises associated with expiration. When a fixed level has been reached, the time is again noted. If the procedure has taken over 70 to 80 seconds, it is likely that the technique was at fault. Most levels are easily obtained within 40 to 60 seconds.

In order further to check the free flow of saline and blood, the manometer is lowered. A prompt rise in the saline level occurs which recedes more slowly when the manometer holder is again leveled off. If the manometer is then elevated, the fluid level sinks. However, it again returns to the venous pressure point, when the manometer is properly adjusted.

The Valsalva experiment ("bearing down" effect) with its increasing the venous pressure and the taking of a deep breath with its lowering the venous pressure were maneuvers not used in determining the true venous pressure. It was found that too often these experiments gave irregular results, sometimes even establishing new venous pressure levels which would last a number of minutes. In order to avoid any diurnal variation, all determinations were made in the late morning before luncheon. The general principle of maintaining basal conditions and avoiding any artificial redistribution of pressure effects, was rigidly adhered to in this study.

When the test is concluded, the syringe, needle and rubber tubing are carefully rinsed free of any blood. Each day the apparatus is used, the manometer is cleaned with bichromate and sulphuric acid solution. This insures smooth running of the fluid column and obviates bubble formation. Periodically, the correction figure for capillary attraction of the saline in use is obtained according to the method of Griffith, *et al.*

The second series of tests were performed with the revised technique on 17 healthy medical students, all under 30 years. The results are presented in Table 2. An average of 4 determinations was made on each subject. The lowest value obtained was 30 mm. of saline; the highest, 100. The average venous pressure for the group was 76 mm. of saline.

The third group similarly studied was comprised of 18 individuals who were over 30 years and gave no signs or symptoms of heart failure. Their data appear in Table 3. An average of 2 tests was done on each case. The extremes in values obtained were 10 mm. and 95 mm. of saline. The average venous pressure for this series was 54 mm. of saline.

TABLE 3.—VENOUS BLOOD PRESSURE IN PERSONS NOT SUBJECT TO HEART DISEASE.

Case.	Age.	Sex.	Diagnosis.	Blood pressure.	Pulse.	Venous pressure (mm. of saline).		Average.
						Right arm.	Left arm.	
31	32	F	No disease	115/80	76	80	85	
				120/80	72	70	70	76
32	30	M	No disease	110/75	84	70	75	
				110/75	72	70	65	70
33	36	F	No disease	120/80	78	90	85	
				125/85	73	95	95	91
34	58	F	Neurodermatitis	160/90	96	60	60	60
35	55	M	Tonsillitis	125/80	72	50	50	50
36	57	M	?Cirrhosis	135/85	72	45	45	45
37	61	M	Epithelioma	130/85	66	25	40	32.5
38	45	M	Tonsillitis	125/85	60	90	90	90
39	54	F	?Ca. stomach	150/90	96	40	55	47.5
40	48	F	Hemoptysis	125/80	120	75	65	70
41	49	F	?Appendicitis	230/120	72	..	75	75
42	55	F	?G. I. malignancy	125/80	72	45	50	47.5
43	40	F	?Pyelitis	140/100	105	45	45	45
44	54	M	Constipation	95/60	72	30	30	30
45	74	M	Ca. rectum	125/80	96	10	10	10
46	80	M	Pharyngitis	120/80	120	50	75	62.5
47	63	M	Diverticulitis, colon	180/110	72	40	..	40
48	46	M	Thrombophlebitis, both legs	150/80	96	30	30	30

Discussion. Among the 108 venous pressure determinations attempted on the 35 cases shown in Tables 2 and 3, there were only 2 failures, 1 due to faulty introduction of the needle into the vein, the other unexplained. This record stands in marked contrast to the 15 failures among the 65 tests done without proper regard for the position of the subject's arm. That this technical detail is important is further substantiated by the fact that 10 of the 15 irregularities occurred in Cases 14 and 15 who later gave perfectly regular results when their arms were supported as shown in the photograph.

In this position also, a lower range of venous pressure was consistently found for cases in general. Thus, the probable explanation for the differences in normal values described by Moritz and Tabora and Griffith, *et al.* rests on the basis of position of the test arm. The figures in Table 1 fall reasonably well in line with those reported by the Griffith group. The values in Table 2 and especially in Table 3 are entirely comparable with those presented by Moritz and Tabora. It is therefore apparent that similar techniques determine similar results. Hence, since the fundamental technique of Moritz and Tabora has proven the more satisfactory in this investigation, the lower range of normal values is considered the more accurate.

It is interesting to note that the average venous pressure for the 18 cases over 30 years was 54 mm. of saline; and for the 17 cases

under 30 years, 76 mm. of saline. For all 35 cases the general average was 65 mm. There was no correlation observed between arterial blood pressure and venous blood pressure. Nor were any significant differences in venous pressure found between the two arms of a given subject.

Summary. 1. Normal venous pressure values obtained by various direct methods are quoted from the literature.

2. Venous pressures of 48 normal subjects determined according to the method of Griffith, Chamberlain, and Kitchel are presented in 3 tables. The first series (Table 1) was studied with the test arm "extended by the side in supination." In the second and third series, the arm was abducted to at least a 70-degree angle and supported approximately as originally described by Moritz and Tabora. It was demonstrated that this single change in a technical detail accounted for greater accuracy in obtaining readings, more consistent results, and a lower range of venous pressure values (Tables 2 and 3).

3. Details of the technique used are given.

4. The normal range of venous pressure thereby obtained in 35 cases was from 10 to 100 mm. of physiologic saline solution, the average value being 65 mm. The older age group tended to have lower levels than the younger.

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THE BODY AS A VOLUME CONDUCTOR AND ITS INFLUENCE ON THE ELECTRICAL FIELD OF THE HEART.

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The assumption that the body is a large, homogeneous conducting medium, forms the basis for much recent work in electrocardiographic analyses. Wilson[8] accepts this fact as conclusive, and

Kossmann[5] in a later publication makes similar deductions. However, the very original methods employed by Smith and Kountz[6] in obtaining an electrocardiogram from a cadaver, connected to an isolated dog heart-lung preparation by means of a shunt, gave evidence that other factors must be considered. Similarly, Katz and Korey[2] deduced from their work that certain tissues conducted impulses better than others, and more recently, Katz, Gutman and Ocko[3,4] reported significant results by altering types of conductors immediately adjacent to the heart.

In the work of Smith and Kountz[6] the gravitating fluids in the body of the cadaver might influence the changes in the records reported by them. The factor of mechanical distortion inherent in the technique employed by Katz and Korey[2] could conceivably explain some of their results. In their later experiments, Katz and his co-workers[3,4] used shunts, the material of which represented such individual variation in the coefficient of conduction, as to find no parallel in the tissues of the body. Thus, there are factors of possible error in the methods pursued by these investigators.

In view of these considerations, we devised a series of experiments to obviate the criticisms mentioned above.

Experimental. The following experiments, examples of repeated procedures, were performed using similar technique throughout. Dogs were used in each instance and one of the Barbiturate compounds intravenously was the anesthetic employed.

Experiment I (Fig. 1). *Shifting the electrode on an extremity produces no appreciable change in the amplitude or the contour of the electrocardiogram.*

The following experiment was performed to prove or disprove this contention:

A. A dog's femoral vein, artery and nerve were isolated. Right arm electrode was inserted in the fourth intercostal space to the left of the sternum. The left arm electrode was inserted in the distal portion of the left leg.

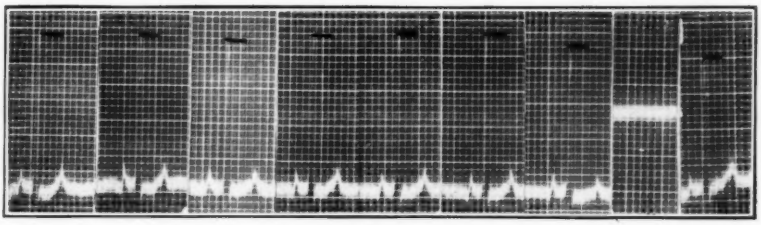
Electrocardiograms were taken after each of the following procedures: (*a*) Control, (*b*) complete circular interruption of the skin in the mid-thigh area, (*c*) ligation of the femoral artery, (*d*) ligation of the femoral vein, (*e*) ligation of the femoral nerve, (*f*) complete severance of the main muscle-mass of thigh, (*g*) periosteum of the femur stripped, (*h*) leg amputated, (*i*) ends of bones brought in apposition.

It will be noted that no appreciable change occurs in the records.

B. The same experiment, severing the structures in reverse order produced comparable results.

Experiment II (Fig. 2). *Altering the contact relationship of lung to chest wall, diaphragm and pericardium.*

Leads I and V (right arm electrode in fourth interspace to the left of sternum; left arm electrode on left leg) were taken as controls. Bilateral, controlled, progressive and simultaneous pneumothorax was performed. Lateral shifting of the heart was thus prevented. Air was introduced into both thoracic spaces simultaneously in quantities from 100 cc. to 600 cc. (Fig. 2).

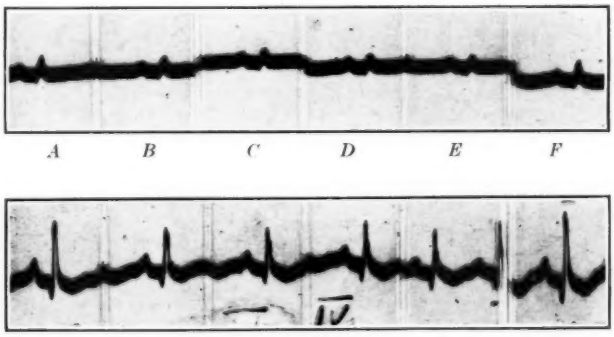


A *B* *C* *D* *E* *F* *G* *H* *I*

(The height of the *R* wave is indicated by a horizontal line.)

FIG. 1.—Experiment I. *A*, Control electrocardiogram. *B*, The skin in the mid-thigh area was completely interrupted and an electrocardiogram taken. *C*, The femoral artery was ligated and severed and electrocardiogram taken. *D*, The femoral vein was ligated and severed and electrocardiogram taken. *E*, The femoral nerve was severed and electrocardiogram taken. *F*, The main muscle mass of the thigh was completely severed to the bone in the mid-thigh region and electrocardiogram taken. *G*, The periosteum of the femur was stripped and an electrocardiogram taken. *H*, The bone was completely severed and the amputated leg held away, no electrocardiogram, of course, registered. *I*, The stumps of the bone were brought in apposition and an electrocardiogram taken.

LEAD I.



A *B* *C* *D* *E* *F*

LEAD XI

FIG. 2.—Experiment II. *A*, Control electrocardiogram. *B*, Electrocardiogram after 100 cc. of air were equally dispersed into the pleural cavities. *C*, Electrocardiogram after 300 cc. of air were equally dispersed into the pleural cavities. *D*, Electrocardiogram after 500 cc. of air were equally dispersed into the pleural cavities. *E*, Electrocardiogram after 600 cc. of air were equally dispersed into the pleural cavities. *F*, Control electrocardiogram after all the air had been withdrawn from both pleural cavities.

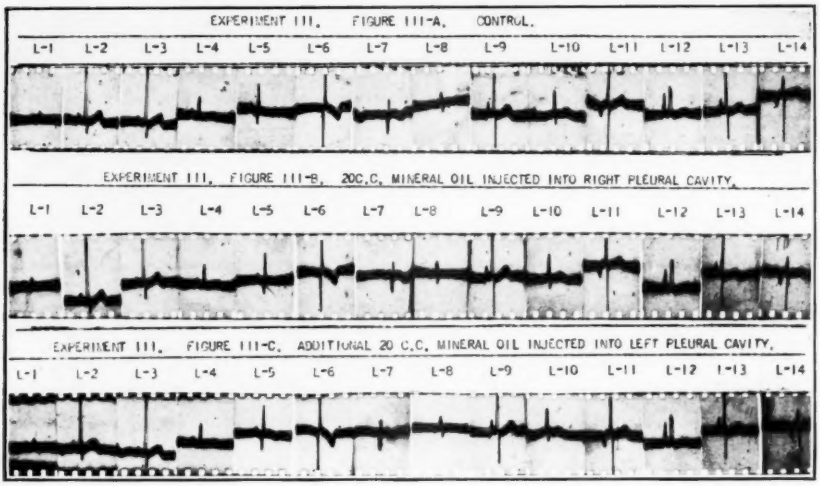

EXPERIMENT III. FIGURE III-A. CONTROL.
L-1 L-2 L-3 L-4 L-5 L-6 L-7 L-8 L-9 L-10 L-11 L-12 L-13 L-14
EXPERIMENT III. FIGURE III-B. 20C.C. MINERAL OIL INJECTED INTO RIGHT PLEURAL CAVITY.
L-1 L-2 L-3 L-4 L-5 L-6 L-7 L-8 L-9 L-10 L-11 L-12 L-13 L-14
EXPERIMENT III. FIGURE III-C. ADDITIONAL 20 C.C. MINERAL OIL INJECTED INTO LEFT PLEURAL CAVITY.
L-1 L-2 L-3 L-4 L-5 L-6 L-7 L-8 L-9 L-10 L-11 L-12 L-13 L-14

FIG. 3.

FIG. 4.—Experiment IV. Right arm electrode in middle bronchus of left lung. Indifferent electrode in left chest. Left chest opened in fourth intercostal space. Left pleural cavity bathed with mineral oil. *A*, Control electrocardiogram. *B*, Electrocardiogram after ligation and severing of left pulmonic veins. *C*, Electrocardiogram after ligation and severing of left pulmonic artery. *D*, Electrocardiogram after ligation and severing of a left bronchial artery.

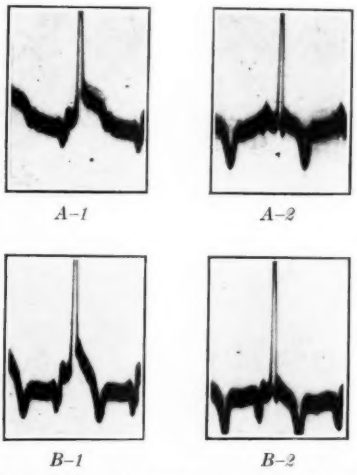
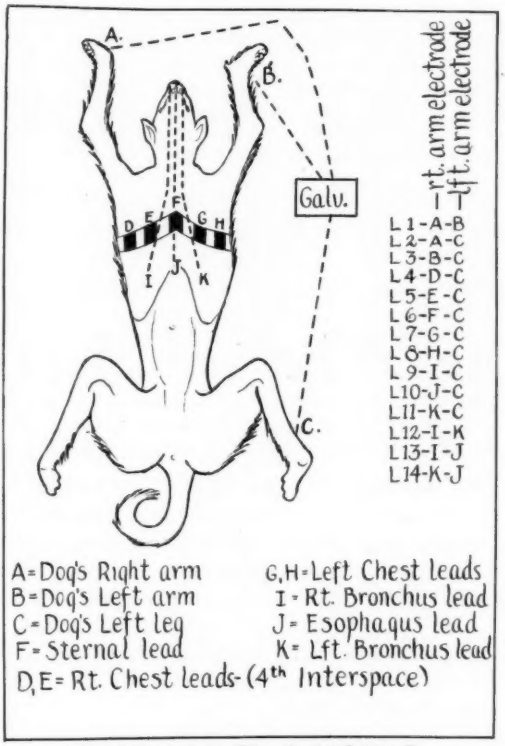


FIG. 5.—Experiment V. Left pulmonary artery ligated and left pulmonary veins isolated and distal and proximal ligatures placed beneath them. *A–1*, Control electrocardiogram with right arm electrode in lower bronchus of left lung and left arm electrode in left leg. *B–1*, Control electrocardiogram with right arm electrode in lower bronchus of left lung 1 cm. removed from that of *A–1* and left arm electrode as in *A–1*. *A–2*, *A–1* repeated after ligation and severing of pulmonary veins. *B–2*, *B–1* repeated after ligation and severing of pulmonary veins.

Noteworthy lessening of voltage in the *QRS* complex, Lead I with increasing intrathoracic pressure is apparent. There is also notching at the apex of this complex. In Lead V there is likewise decrease in voltage of *QRS* wave and notching, which tends to shift from its apex toward the isoelectric line with increase in air pressure.



EXPERIMENT III - DIAGRAM I.

Experiment III (Fig. 3, A. B. C. Diagram I). *Complete insulation of the lungs without changing intrathoracic relationships or altering intrathoracic pressure.*

A. Three standard electrocardiograms were recorded. Successive control records were made by leading off from thorax, lungs and esophagus* as indicated in Diagram I.

B. 20 cc. Mineral oil† were injected into the right pleural cavity and same 14 leads taken as in *A*.

C. 20 cc. Mineral Oil were injected into the left pleural cavity and same leads recorded.‡

* Esophagus and intrabronchial electrodes consisted of long well insulated wires with a small hook at the contact point. They were placed *in situ* by means of a bronchoscope. Contact electrodes were of the same material for any given experiment.

† Squibb, Resistance of this oil, measured between plates 3 mm. apart, equivalent to at least 600,000 ohms per sq. cm. through one millimicron thickness.

‡ At autopsy, on examining the tissues with hand lens, no break could be found in oil film surrounding visceral and parietal pleura.

In none of these curves is there any change in amplitude or contour. Thus, the lungs do not appreciably transmit the current to the surface of the body and must receive their potential through their pedicles.

Experiment IV (Fig. 4). *The pedicles of the lung as transmitting media of current from the heart.*

A dog was anesthetized. Right arm electrode placed in the middle bronchus of the left lung, the left arm electrode being placed in the left leg. Under positive pressure, the left chest was incised at the level of the fourth interspace, pulmonic veins, left pulmonic artery and a bronchial artery of the left bronchus were isolated and ligatures placed *in situ*. The pleural cavity was then bathed in oil and records taken after successively ligating and severing the individual vessels.

The changes noted in the various components of the electrocardiogram are definite. They can hardly be explained by increased pressure in the left ventricle.

Experiment V. Elimination of the possible factor of increase in ventricular pressure as a source of error.

Experiment IV was repeated, with the exception that two right arm electrodes were placed in the lower bronchus of the left lung (1 cm. apart) with the indifferent electrode on the left leg. The bronchial veins were isolated and ligatures placed *in situ*. The pulmonary artery was ligated distally and proximally and two electrocardiograms taken (Fig. 5, A-1 and B-1). The pulmonary veins were then tied and cut (Fig. 5, A-2 and B-2).

Results. The findings recorded in the first experiment are not difficult to understand. The various tissues excised are known to be excellent conductors. When the amputated part of the leg was allowed to remain on the operating table quite appreciably apart from the stump, but bathed in the same blood, the curves were not altered. *The extremities, therefore, do act as volume conductors, not only because of the relatively good conduction of each of the structures,* in contrast to the galvanometer circuit, but *also because of their remoteness from the heart.*

Approaching the problem by interfering with the several pathways in the vicinity of the heart over which the current might pass from the heart to the periphery, some noteworthy facts were disclosed. Almost insuperable difficulties were encountered in attempting to conserve the normal relationships in the chest and thus prevent a shift in axis of the heart or disturbance of lung contact. Experiment II, although carefully controlled by injecting air into the two chest cavities simultaneously, and by the use of the fluoroscope, is still subject to possible error. The chambers of the heart and the great vessels are not equally resistant and might react unequally to the same pressure. Then, too, one cannot be sure the heart has not rotated with removal of its support by the lungs.

To obviate this, Experiment III was performed which insulated the lungs without increasing intrathoracic pressure. Moreover, the leads were taken from the inner aspect of the lungs as well as the outer surface. The resultant records do not indicate decrease of

amplitude or change in contour of the curves. Thus, the lung pedicles alone remain as selective paths for the current conduction, and in the last two experiments (IV and V) this fact is disclosed (Figs. 4 and 5). These electrocardiographic changes are definite and distinct. Could these changes be due to disturbances in arterial or ventricular pressure? As far back as 1876, Lichtheim[7] and somewhat later, Tigerstedt, demonstrated that three-fourths of the total number of branches of the pulmonary artery could be ligated, before arterial pressures were affected. Further, it has been shown that the lumen of the pulmonary artery could be compressed up to 60% of its capacity without affecting arterial pressure (Haggard and Walker[1]). On the other hand, Wiggers[7] observed changes in pressure within the right ventricle following the ligation of a single branch of the pulmonary artery.

In the last experiment (V) this possible factor is eliminated because that portion of the circulatory system is interrupted which could increase right intraventricular pressure. The deduction is, therefore, that *the electrocardiographic changes noted after ligation of various components of the lung pedicle represent interference with the passage of current through these tissues.* The pedicles offer paths of selection for the transmission of current from the heart to the lungs.

Conclusions. 1. Visual evidence is presented to confirm the accepted fact that the extremities act as volume conductors of the electrical potential generated in the heart.

2. The lungs transmit none of the differences in electrical potential registered in the electrocardiograms obtained by surface leads.

3. The lung pedicles act as the sole bridge for transmission of current to the lungs.

4. These pedicles offer selective pathways of conduction.

5. The recent controversies as to the advisability of using the apex of the heart or the fourth interspace just to the left of the sternum for the site of preference of the right arm electrode in Leads IV and V, seem to accept, *a priori*, the dictum that the chest is a volume conductor. We are convinced that the discrepancies seen in these controversies can be explained on the basis that the chest is not a volume conductor.

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THE PROGNOSIS IN "POTENTIAL RHEUMATIC HEART DISEASE" AND "RHEUMATIC MITRAL INSUFFICIENCY."

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The prognosis of patients having an obvious diagnosis of rheumatic cardiac valvular deformity has been fairly well elucidated by many statistical studies. The prognosis, however, of young patients between the ages of 12 and 30 years, who have had rheumatic fever or chorea and present on physical examination either an entirely normal heart or at most an apical systolic murmur, has been far less thoroughly explored. The greatest diversity of views is found among the available statistical material in the literature as to the relative influence of chorea and of rheumatic fever in producing valvular lesions,[2] and few guides have been set up to indicate the probable future course of patients with slight rheumatic valvular damage.

These discrepancies in our knowledge have been in the main the result of two difficulties: the faulty memories of older patients with respect to their early rheumatic histories, and the difficulty of trying to follow closely a large group of essentially well people over a long period of years. However much the relative significance of a rheumatic history or of a systolic heart murmur may have been debated by clinicians in the past,[4] the large statistics of life insurance companies show that they have a definite influence on mortality rates.[1] It seemed worth while, therefore, to collect and analyze the records available in the cardiac clinic of this hospital as a contribution toward the evaluation of various factors operating in the production of chronic cardiac valvular disease.

Material. The present analysis consists of 225 cases with a history of rheumatic fever or chorea, but showing when first seen either nothing or at most a systolic murmur in the heart. Practically all patients were between 12 and 20 years when first seen (an average age of 13.8 years). With few exceptions the group consisted of patients who had had their rheumatic fever or chorea in a children's hospital, had been followed in a cardiac clinic there and then referred to our clinic upon reaching the age limit of 12 years, or who had been seen in this hospital with their first rheumatic infection and were subsequently followed in our clinic. Ten of the cases were referred to the clinic by school physicians because of the discovery of a heart murmur, but with no definite history of rheumatic fever or chorea and with the possibility of congenital heart disease being ruled out as far as possible. The onset of rheumatic infection was then assumed to coincide with the first discovery of the murmur.

The histories, therefore, are probably as reliable as is possible in such a series. All cases who had had severe cardiac damage with their earlier rheumatic infection were excluded. Patients with no clinical evidence of rheumatic activity were seen at intervals of 6 months to 1 year, and those suspected of activity, at shorter intervals. During flare-ups of rheumatic activity they were either placed in bed at home if the flare-up were mild, or in hospitals or convalescent homes for long periods if more severe. These patients then have had the best available supervisory care for the clinic class of rheumatic patients. The average length of time over which the 225 patients were seen in this clinic was 9.6 years (Table 1).

TABLE 1.—LENGTH OF TIME CASES WERE FOLLOWED.

Cases.	Time, years.	Average, years.
96 (41.8%)	1 to 4	2.7
91 (40.9%)	5 to 9	6.9
29 (13.2%)	10 to 14	11.6
5 (2.3%)	15 to 19	16.4
4 (1.8%)	20 to 23	22.0

For purposes of comparison, however, the patients were divided into groups expressing the years elapsed between each patient's first attack of rheumatic fever or chorea and his last visit to our clinic, which indicates the numer of years the rheumatic state may have existed in each patient, and it was upon this basis that the remaining analyses of this series were made (Table 2). The average time elapsed since the first attack of rheumatic fever or chorea for the whole group of 225 cases was 9.2 years. The sex distribution was 40% males, 60% females.

TABLE 2.—LENGTH OF TIME BETWEEN FIRST ATTACK AND LAST VISIT TO CLINIC.

	1–4 yrs.	5–9 yrs.	10–14 yrs.	15–19 yrs.	20–23 yrs.
No. of patients	32	95	72	20	6
Per cent of patients	14.2%	42.2%	32.0%	8.9%	2.7%
Average time elapsed	3.0 yrs.	7.0 yrs.	11.9 yrs.	16.5 yrs.	21.7 yrs.

Diagnostic Criteria. *Potential Rheumatic Heart Disease.* Patients with a history of rheumatic fever or chorea, but showing on examination either a normal heart or only a systolic murmur, if persistent, of not more than "Grade 1 intensity",[3] were regarded as having potential rheumatic heart disease.

Rheumatic Mitral Insufficiency. Patients with a history of rheumatic fever or chorea, and showing on physical examination a persistent apical systolic murmur of "Grade 2 intensity" or more were considered to have rheumatic mitral insufficiency. Those who showed at any time a systolic murmur which later disappeared were included under "potential rheumatic heart disease." Though our practice of grading the intensity of systolic murmurs has been in use only a few years, we have a fairly definite clinical impression that Grade 1 systolic murmurs frequently disappear later, and Grade

2 murmurs occasionally, but that Grade 3 murmurs are almost always persistent over many years.

Aortic Insufficiency. The prerequisite for this diagnosis was a persistent early diastolic bruit of any intensity at the base of the heart or along the left sternal border. In cases showing this diastolic murmur alone there is little doubt that it represented aortic insufficiency. In those also having mitral stenosis, the possibility of its being a "Graham Steele murmur" might be argued in some cases. Inasmuch as none of our cases were in failure such confusion can be disregarded.

Aortic Stenosis. This diagnosis was made in only one rheumatic patient who had an enlarged heart, aortic insufficiency and a loud, rough (Grade 4) systolic murmur and accompanying thrill in the second right intercostal space near the sternum.

Mitral Stenosis. The review of this series of cases emphasized the necessity of being conservative in making this diagnosis, a view which is to be elaborated in another paper by the authors. The diagnosis was made in cases with a regular heart rhythm on the basis of a rough mid to late diastolic or presystolic crescendo murmur ending in an accentuated first sound at the apex, or in cases with auricular fibrillation on the basis of a low pitched apical diastolic murmur of any duration. Cases with regular rhythm and low pitched apical diastolic murmurs shorter than the classical crescendo type and without marked accentuation of the first sound were labelled "question of mitral stenosis" unless the murmur had been present at least 4 years. A special effort was made to exclude the "normal third heart sound" from the latter category.

Tricuspid Insufficiency or Stenosis. No case suggesting tricuspid valve deformity was encountered in this series.

Only two members of the series are known to be dead, though many have been lost sight of for other causes. One case of mitral stenosis died suddenly in another hospital of acute pulmonary edema or pulmonary embolus. No autopsy was obtained. Another case of mitral stenosis and insufficiency and aortic insufficiency died in this hospital of subacute bacterial endocarditis. Postmortem examination confirmed the diagnosis.

Potential Rheumatic Heart Disease. This was the diagnosis made in 166 patients (73.8% of the series) on the basis of a normal heart when first admitted to the clinic or the subsequent disappearance of systolic murmurs originally present. In Table 3 these cases are compared according to the years elapsed since their first attack to ascertain the relative effect of single and repeated attacks of rheumatic fever or chorea in producing valvular deformity. Individual attacks of rheumatic fever and/or chorea within one year of each other are treated as a single attack.

It is evident that of 166 cases labelled "potential rheumatic heart disease," only 8 (4.8%) subsequently developed recognizable valve disease or a serious question of it. It is interesting that there

seemed to be little difference in this respect between single and repeated attacks, the latter having only a slightly higher incidence of valve deformity. This would seem to indicate that following a single attack of rheumatic fever or chorea those patients who could be diagnosed "potential" had about a 96% chance of escaping valve disease, and if after 5 years following the attack nothing new developed, then there was practically 100% chance of their escaping serious cardiac damage. Following repeated attacks, the chances when the diagnosis was made were 94% if less than 10 years had elapsed since the first attack, and 100% after 10 years. It is difficult to escape the additional conclusion that these "potentials" formed a group whose hearts were relatively resistant to rheumatic infection.

TABLE 3.—POTENTIAL RHEUMATIC HEART DISEASE.

	1–4 yrs.	5–9 yrs.	10–14 yrs.	15–19 yrs.	20–23 yrs.	Totals.	
Cases remaining potential after a single attack	19	41	22	9	3	94	158
Cases remaining potential after repeated attacks	4	25	27	7	1	64	
Potentials after single attack who later showed permanent lesion*	2 ?2	..	..	..	..	4	8
Potentials after repeated attacks who later showed permanent lesion*	?1	3	..	..	..	4	

* Aortic insufficiency, mitral stenosis or questionable mitral stenosis (?2 = 2 questionable cases of mitral stenosis). The time interval shown is the time between the first attack and the appearance of the lesion.

Rheumatic Mitral Insufficiency. This group of 59 cases (26.2% of the series) presented on physical examination a persistent apical systolic murmur of sufficient intensity to warrant a diagnosis of mitral insufficiency. The effects of single and repeated attacks of rheumatic fever and chorea are compared for this group in Table 4.

TABLE 4.—RHEUMATIC MITRAL INSUFFICIENCY.

	1–4 yrs.	5–9 yrs.	10–14 yrs.	15–19 yrs.	20–23 yrs.	Totals.	
Persistent M.I.* alone following single attack	4	8	7	2	..	21	34
Persistent M.I.* alone following repeated attacks	1	8	4	..	..	13	
M.I. following single attack who later showed permanent lesion†	3 ?1	?1	..	..	..	5	25
M.I. following repeated attacks who later showed permanent lesion†	5 ?3	4 ?1	4 ..	2 ?1	..	20	

* Mitral insufficiency.

† Aortic insufficiency, mitral stenosis or ?mitral stenosis.

It is apparent that 34 (58%) of the cases of mitral insufficiency persisted virtually unchanged throughout the period of observation, while 25 (42%) subsequently developed serious valvular disease or a strong probability of it. Of the 26 cases showing mitral insufficiency following a single attack, 5 (19%) developed a serious

lesion, all within 5 years after the infection. Of the 33 cases of mitral insufficiency with a history of repeated attacks, 20 (61%) later developed other definite or strongly probable valvular lesions, and the appearance of the lesions was fairly well scattered throughout the 20 years following the first attack. Therefore, patients showing mitral insufficiency following a single attack had an 81% chance of escaping further lesions under 5 years of observation, and 100% after 5 years. Similar patients with a history of repeated attacks, however, had only a 39% chance of escaping under 5 years after the first attack, with a progressively better prognosis the further removed from the initial attack during the next 20 years.

Relative Influence of Rheumatic Fever and Chorea. In an attempt to evaluate the relative effect of rheumatic fever and chorea in producing valvular damage, the cases in this series that developed unquestionable signs of mitral stenosis or aortic insufficiency or both were compared with the entire series, according to their histories (Table 5).

TABLE 5.—CASES DEVELOPING UNDOUBTED MITRAL STENOSIS OR AORTIC INSUFFICIENCY.

Following a single attack of rheumatic fever	3
Following a single attack of chorea	0
Following repeated attacks of rheumatic fever	9
Following repeated attacks of chorea	3
Following one or more attacks of both	9
No history of rheumatic fever or chorea	2

History.	Cases in entire series.	Cases developing M.S., A.I., or both.	%.
Chorea alone	44	3	6.8
Rheumatic fever alone	122	12	9.8
History of both	49	9	18.4
History of neither	10	2	20.0

The high percentage of valvular disease developing in the group with no history of rheumatic fever or chorea is obviously fallacious because these patients were all sent in to the clinic because of a definite suspicion of heart disease, whereas the remainder were followed simply because they had a history of chorea or rheumatic fever. It is then seen that the combination of chorea and rheumatic fever in the history was followed by much the highest percentage of valvular damage (18.4%), while that following rheumatic fever alone was not conspicuously higher than that following chorea alone (9.8 and 6.8%). It is interesting that in no instance did subsequent valvular damage follow a single attack of chorea. This might be construed as support for the contention[2] that chorea alone is incapable of producing rheumatic heart disease unless accompanied by rheumatic fever, even though the latter might be so mild as to be clinically unrecognizable. But the very much higher incidence of valve disease following a combination of rheumatic fever and chorea than from either alone (it is in fact about equal to the sum of the

two diseases considered separately) might also support the view that there may be a "non-rheumatic chorea" indistinguishable clinically from the "rheumatic form." In this event, however, we believe that repeated chorea should probably always be regarded as of the "rheumatic form."

Relative Susceptibility of Valves in Relation to Sex. The well-known tendency of the mitral valve to be involved in females and the aortic valve in males was shown clearly in this series, though the total valvular involvement was about equal in the two sexes as shown in Table 6 (60% of the series were females).

TABLE 6.—VALVULAR INVOLVEMENT IN RELATION TO SEX.

	M.S.	A.I.	M.S. + A.I.	A.I. + A.S.	Total.
Males	3	5	2	0	10 (38.5%)
Females	9	3	3	1	16 (61.5%)

The theory has been advanced that the reason for the higher incidence of mitral stenosis in females may be that chorea is more likely to produce mitral stenosis than is rheumatic fever, and that chorea is more common in females. To investigate this possibility the cases of undoubted mitral stenosis, with or without aortic insufficiency, were analyzed according to history and sex and compared with a similar analysis of the entire series (Table 7).

TABLE 7.—COMPARISON OF MITRAL STENOSIS CASES WITH THE ENTIRE SERIES.

	Males.			Females.		
	Entire series.	M.S.	%.	Entire series.	M.S.	%.
Chorea alone	15	0	0.0	29	3	10.0
Rheumatic fever alone	57	3	5.3	65	3	3.1
History of both	15	1	6.7	34	5	14.7
History of neither	3	1	33.3	7	1	14.3

Again disregarding those cases with no history, it is seen that chorea or combinations of chorea with rheumatic fever were much more frequently followed by mitral stenosis in females than in males, while the incidence following rheumatic fever alone was somewhat greater in males than in females. This would seem to furnish some support to the above explanation of the more common occurrence of mitral stenosis in females.

There are some general practical inferences to be drawn from the above survey. One is led to the impression that the term "potential heart disease" is a valid term, for if after an attack of rheumatic fever or chorea there is no murmur or only a very faint systolic murmur (Grade 1), that patient stands an excellent chance of remaining well for many years. This is particularly true if the negative findings persist after 5 years. We have the distinct impression that some of these cases, however, even without any subsequent clinical recurrence of rheumatic fever, will develop mitral stenosis 10, 20 or 40 years later. This opinion is based on the experience of observing patients 50 or 60 years of age and older, who had their only rheumatic bout in childhood, first became aware of any heart trouble and showed signs of typical mitral stenosis at an advanced age.

Another point of interest is the subsequent course of those cases designated as having rheumatic mitral insufficiency on the basis of an apical systolic murmur of Grade 2 intensity or louder. We believe that although some will carry on indefinitely without any significant cardiac disability, some if not many will inevitably develop subacute bacterial endocarditis. These cases form a not insignificant group of patients who remain well for a great many years who may have been aware that they had a "harmless" murmur but who eventually pick up the fatal form of bacterial endocarditis. A few will slowly progress and develop mitral stenosis and others who only showed an apical systolic murmur may be found to have typical aortic stenosis many years later.

Summary and Conclusions. From an analysis of 225 cases of "potential rheumatic heart disease" and "rheumatic mitral insufficiency" followed for an average of 9.6 years the following conclusions were drawn:

1. Of those cases diagnosed "potential rheumatic heart disease," 4.8% subsequently developed mitral stenosis, aortic insufficiency or both. With a history of only a single attack of rheumatic fever or chorea, these patients had a 96% chance of escaping valvular disease during 5 years after the attack, and 100% after 5 years. With a history of repeated attacks, the chances were 94% if less than 10 years had elapsed since the first attack and 100% after 10 years.

2. Of those cases diagnosed "mitral insufficiency," 58% persisted unchanged throughout the period of observation, while 42% subsequently developed mitral stenosis or aortic insufficiency. Those with a history of a single attack of rheumatic fever or chorea had an 81% chance of escaping further lesions before the lapse of 5 years, and 100% after 5 years. With a history of repeated attacks their chances were only 39% if less than 5 years had elapsed since the first attack, with a progressively more favorable prognosis as further years passed without the development of other lesions.

3. The occurrence of both rheumatic fever and chorea in the history was followed by a much higher incidence of valvular damage than following either disease alone, while that from rheumatic fever alone was about equal to that from repeated chorea alone. There were no instances of valvular disease following a single attack of chorea.

4. Some support was found for the theory that the greater tendency of chorea to produce mitral stenosis and the higher incidence of chorea in females is the explanation of the more frequent occurrence of mitral stenosis in females than in males.

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TRANSIENT NODAL RHYTHM FOLLOWING USE OF SULPHANILAMIDE.

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While it appears that sulphanilamide (para-aminobenzene-sulphonamide) has been established as a valuable therapeutic agent in combating infections due to hemolytic streptococci and some of the Gram-negative cocci, its ultimate range of use rests largely upon the severity and frequence of toxic effects. Among the ill-results caused by sulphanilamide have been reported: irritant effect on tissues of the urinary tract,[1] acidosis and depression of liver function (as determined by bromsulphalein),[7] neutropenia,[5] cyanosis, sulphemoglobinemia,[2] acute hemolytic anemia,[4] jaundice and urticaria,[6] and so on.

There have been no reports indicating a possibility of cardiac damage from sulphanilamide. In order that we may be able properly to select our patients to whom we plan to administer this drug, it is important that we record any adverse reactions. In addition to the aforementioned undesirable results, the writer presents a case which might establish the likelihood of cardiac damage resulting from the use of sulphanilamide.

Case Report. H. F., a physician, aged 27, had been suffering from an acute sore throat for 1 day. Throat culture revealed about 90% beta-hemolytic streptococci. Of his own accord, he took 80 grains of Prontylin (sulphanilamide) in 1 dose. Approximately 3 hours later he became nauseated, felt dizzy and had tinnitus aurium. He took 1½ grains of phenobarbital and went to bed. On the following morning, February 1, 1937, I was summoned to see him and he was complaining of pains in his knees and elbows, and in the small joints of his feet. There was no soreness of the throat.

The temperature was 98.6° F., pulse 80 and respiratory rate 20 per minute. The patient did not look ill. The general physical examination revealed very few abnormalities. The mucous membranes were of good color. There was no cyanosis or jaundice. The throat was slightly red, but did not appear acutely inflamed. Tonsils were absent. No enlargement of the cervical glands. The heart was normal in size. There was a soft systolic murmur heard over the entire precordium, but was loudest over the mitral area. The rhythm was regular. The lungs were clear to percussion and auscultation. The liver and spleen were not palpable. Weight, 160 pounds (72.7 kg.). No objective signs of joint disease.

The laboratory studies revealed the following: Throat culture: 90% beta-hemolytic streptococci. Blood: Red blood cells, 5,370,000; hemoglobin, 13.3 gm.; white blood cells, 9700. Neutrophils, 73%; lymphocytes, 22%; monocytes, 5%. Schilling count—stabs, 10; segmented, 63. Blood sedimentation (Cutler method) 15 mm. diagonal line.

Blood uric acid, 2.4 mg. per 100 cc. Urine: Specific gravity 1.007, faint trace of albumin, no sugar, acetone or diacetic acid, sediment normal.

He was placed on medical treatment administering large doses of salicylates for the joint pains. Felt quite comfortable, no sore throat, joint pains

subsiding. On February 4, 1937, the patient became "cardiac conscious" and complained of irregularity in rhythm. Dr. E. H. Campbell was asked to do a complete otolaryngologic examination and he reported that the left maxillary sinus was slightly cloudy, the right one very cloudy, and the pharynx congested and showed evidence of excessive lymphoid tissue. The same day the temperature rose to 101°, pulse, 100, respirations 22.

Laboratory Studies: Blood: Red blood cells, 5,150,000; hemoglobin, 14 gm.; white blood cells, 14,400. Neutrophils, 66%; lymphocytes, 23%; monocytes, 11%. Schilling count—stabs, 12; segmented, 54. Sedimentation of red cells, 25 mm. Diagonal curve. Roentgen ray Studies: Heart normal size and contour. Lungs, negative; Teeth, upper right first molar showed evidence of some absorption of apices of roots.

The patient's general condition improved rapidly and he felt perfectly well, excepting that he was always conscious of some irregularity in cardiac rhythm. Discharged from the hospital February 10, 1937. Studies at the time of discharge: Temperature 98.2° F., pulse 70, respirations 18. Blood: Red blood cells, 5,300,000; hemoglobin, 13.8 gm.; white blood cells, 7600. Neutrophils, 67%; lymphocytes, 27%; monocytes, 4%; eosinophils, 1%; basophils, 1%. Schilling count—stabs, 9; segmented, 58. Sedimentation of red cells, 23 mm. Diagonal curve.

Patient went to Florida for 2 weeks' vacation and returned feeling well, but still complained of cardiac irregularity. Electrocardiographic tracings were done frequently and the findings were practically the same, in that there was a persistence of low voltage and nodal premature contractions.

No irregularity in rhythm was noted after April 20, 1937. The last tracing was taken on June 8, 1937, and is hereby presented to show return of normal rhythm, but evidence of myocardial degeneration persists.

During follow-up studies the blood pressure fluctuated from 130/80 to 160/90. Urine concentration studies (No. 1) 1.020, (No. 2) 1.019, (No. 3) 1.022. Eyegrounds by Dr. E. B. Spaeth: "Light streak on arteries of right eye more pronounced than normal. Increased tortuosity of vessels of smaller dimensions."

Comment. In view of the evidence that the patient was suffering from an infection, one naturally would wonder if the myocardial changes were not secondary to the infection. However, since there were definite symptoms of toxicity or idiosyncrasy after the ingestion of the drug, and since the one single dose was larger than is customarily prescribed, one seems justified in emphasizing the possibility of cardiac damage from the use of sulphanilamide. Also previous sore throats prior to the advent of sulphanilamide failed to cause any cardiac irregularity.

It is granted that the evidence presented is insufficient to prove definitely that sulphanilamide is capable of producing cardiac arrhythmias or cardiac damage. On the other hand, Griffith[3] had 2 cases that developed arrhythmias while taking sulphanilamide, which disappeared when the drug was discontinued. When Ratcliffe* gave a closely allied drug—Setazine (para-benzylaminobenzenesulphonamide) to a flamingo (weight 7 kg.) at the Philadelphia Zoölogical Gardens for a streptococcic ulcer on the thigh (5, 10 and 15 grains over 3 days), he found marked myocardial degeneration which he regarded as the cause of death.

* H. L. Ratcliffe, Ph.D., Assistant Pathologist, Penrose Research Laboratory, Philadelphia Zoölogical Gardens.

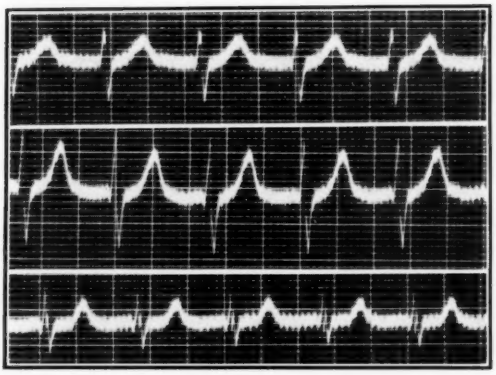

FIG. 1.—Tendency to right axis deviation, auriculo-ventricular nodal rhythm with the *P* waves coming after *QRS*, superimposed on *T*. Rate 118. (2/5/37).

FIG. 2.—Note nodal premature contractions. (3/23/37).

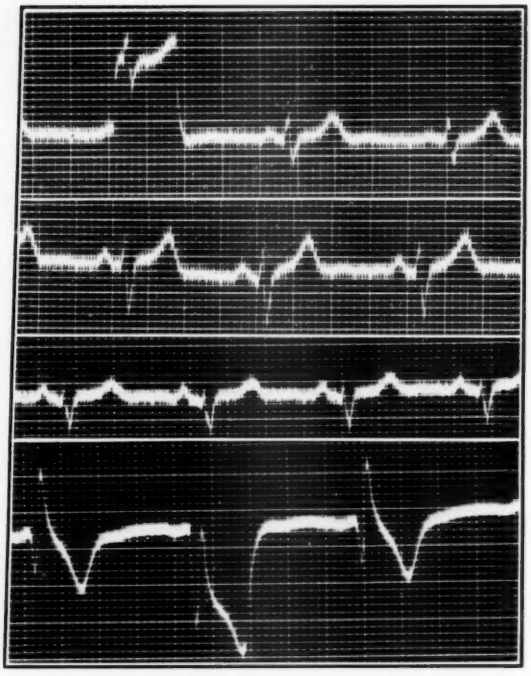

FIG. 3.—Note low voltage and normal rhythm. (6/8/37).

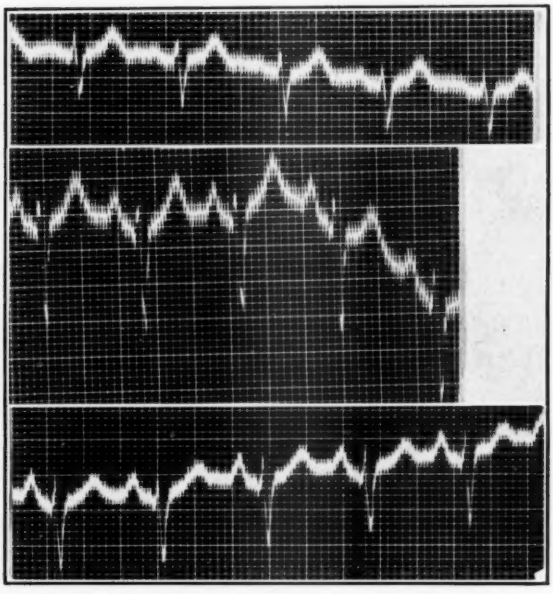

FIG. 4.—Note normal voltage. (1/23/34).

The patient here reported had, during his student days, occasionally developed attacks of paroxysmal tachycardia. An electrocardiogram taken at that time (January 23, 1934), is included for comparison with those taken after the ingestion of sulphanilamide.

The fact that the patient had manifested evidence of disturbance or irritability of the cardiac conductive system prior to having taken sulphanilamide, suggests that perhaps sulphanilamide is not apt to alter the rhythm unless there is some preëxisting irritability of the conductive system.

Summary. A case is presented of a physician who had taken 80 grains of Prontylin (para-aminobenzenesulphonamide) in 1 dose, which were followed by transient symptoms. Four days thereafter he developed arrhythmia and electrocardiograms revealed signs of myocardial degeneration and nodal rhythm.

Other evidence is cited to support the possibility that sulphanilamide is capable of producing myocardial damage.

While the evidence is insufficient to prove definitely that sulphanilamide was responsible for the cardiac disturbance in the patient herein reported, it indicates the need for caution in its administration to patients with cardiac disease, until further experiences are recorded.

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MANIPULATION OF GLUCOSE TOLERANCE BY DIET.

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The tolerance which an individual develops for glucose depends to a large degree upon the diet to which he has become accustomed. In the diabetic patient, the low tolerance for glucose may be increased by the use of a diet high in carbohydrate. In individuals with chronic hypoglycemia and increased glucose tolerance, there is a diminution in tolerance following restriction of intake of carbohydrate.

Hamman and Hirschmann[4] showed that in normal individuals "the ingestion of glucose in some way stimulates the mechanism of carbohydrate disposal so that the repeated ingestion of the same

amount, causes a less marked hyperglycemia. The same stimulating effect is noted in diabetes; the second dose is followed by a less marked hyperglycemia and glycosuria. However, the difference between the effects of the two doses is less marked than in normals and varies in different stages of the disease."

It was demonstrated by Sweeney[7] and later by Himsworth[5] that in normal individuals the restriction of carbohydrate in the diet is followed by a loss of tolerance for glucose, whereas a diet high in carbohydrate results in an increase in tolerance.

Both Sweeney[7] and Greisheimer *et al.*[3] called attention to the fact that the glucose tolerance test is significantly affected by the character of food taken prior to the test.

The observations of Ellis[1] are very interesting in respect to the glucose tolerance in severe diabetes. In a small series of cases Ellis gave insulin at hourly intervals and glucose orally in amounts as high as 600 gm. per day. In all instances there was a striking reduction in the insulin requirement as compared to the doses necessary on a previously moderately restricted diet. There was a greater response in the younger, ill-adjusted patients than in the older and better adjusted ones. In this connection our own observations have shown repeatedly the necessity of lowering the insulin dosage in diabetic subjects receiving continuous intravenous glucose therapy.

Gibson[2] showed that diabetics who were controlled on a low carbohydrate maintenance diet had a remarkable improvement in tolerance, as indicated by a lessened requirement for insulin following 2 or 3 days of high sugar ingestion with increased insulin. Furthermore, he found that successive periods of high sugar diet at intervals of 4 or 5 days usually resulted in a progressive increase in tolerance, as judged by insulin requirements.

Weeks, Renner, Allen, and Wishart[8] placed 6 epileptic patients on very high fat, extremely low carbohydrate diets for 48 days. In every patient hyperglycemia gradually developed. The highest figure reached was 357 mg. per 100 cc.

Although the clinical implications are obvious both in respect to the dietary management of diabetes and of hypoglycemia, it is not the purpose of this paper to discuss in detail the practical application of these observations. We wish simply to show to what degree the glucose tolerance curve is altered as the result of diet in various conditions.

Two small groups of unselected cases are presented. Group 1 is comprised of 7 cases of chronic hypoglycemia. Glucose tolerance curves are employed to show that the use of low carbohydrate, high fat diets is followed by a decrease in tolerance and relief of symptoms. In such cases the tolerance tests show definite, and in some instances quite marked, elevation of blood sugar levels. In 2 subjects these rose to within diabetic range and were associated with glycosuria. In 1 of these patients whose intake of carbohydrate was subse-

quently raised, the sugar curve promptly fell again to within normal range.

Group 2 demonstrates marked improvement following the use of high carbohydrate diets in 5 cases of mild diabetes, as shown by glucose tolerance tests before and after treatment. In these cases all but 2 patients had not been controlled previously and this might have influenced the degree of change. One member of this group, after having been controlled on a high carbohydrate diet, was given a low carbohydrate, relatively high fat diet of equal caloric value and, after a month, a glucose tolerance test yielded distinctly higher blood sugar levels.

The dextrose tolerance test used in our cases is as follows: In the morning the fasting subject is given orally 100 gm. of glucose in 200 cc. of water and then only water is permitted until the completion of the test. Estimations of the blood sugar are made on the fasting blood and at intervals of ½, 1, 2, 3, and 4 hours after the ingestion of glucose, specimens of urine being obtained for estimation of sugar at the same intervals. At each of these times, an additional 300 cc. of water is given to insure the excretion of sufficient urine. Standard anticoagulants (calcium oxalate and sodium fluoride) are used and the blood sugar determinations are made on 1 cc. samples by a modified Myers-Bailey method.[6]

The cases studied are briefly summarized.

Case Abstracts. *Group 1.* Case 1 (Fig. 1).—A man of 42 with a tentative diagnosis of hyperthyroidism had not improved following iodine therapy. This patient complained that nervousness, palpitation, tachycardia, dyspnea, and fatigue had been present for 1½ years. He had lost 20 pounds in weight over a period of 14 months. Examination revealed cool, moist, cyanotic hands and feet, tachycardia, and digital tremor. The basal metabolic rate was −8%.

He failed to improve on a schedule of rest, sedation, and high vitamin, high caloric diet. When he was seen again 6 weeks later, it was recognized that the symptoms usually occurred several hours after a meal. The glucose tolerance test showed evidence of increased tolerance, although 0.3 gm. of sugar was excreted between the first and second hour. His symptoms were reproduced by the injection of insulin.

A high fat, low carbohydrate diet (C. 85, P. 74, F. 180, Cal. 2256) was given and the tolerance test was repeated in 1 month, at which time he was clinically improved. This curve showed definite diminution in tolerance, but still a terminal hypoglycemia. Two months later he was symptom-free and "feeling better than for many years." The tolerance curve then was definitely of diabetic type, the 1-hour sugar level being 333 mg. per 100 cc. with no terminal hypoglycemia and a total glycosuria of 6.3 gm.

Case 2 (Fig. 2).—In September, 1935, a woman of 41 presented herself, with severe headaches and attacks of upper abdominal pain. Weakness had been a prominent symptom recently and this was aggravated by short periods of perspiration, nervousness, and trembling. In June, 1935, a diet of C. 180, P. 56, and F. 75, Cal. 1619 had been prescribed elsewhere. A glucose tolerance test on July 14 showed a greatly increased tolerance for glucose. The glucose tolerance test repeated on September 6, 1935, gave

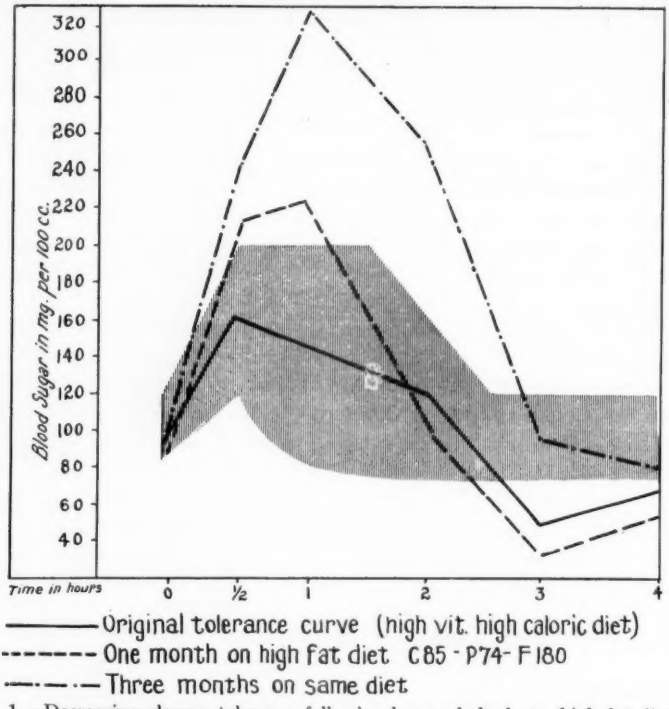

FIG. 1.—Decreasing glucose tolerance following low carbohydrate, high fat diet.

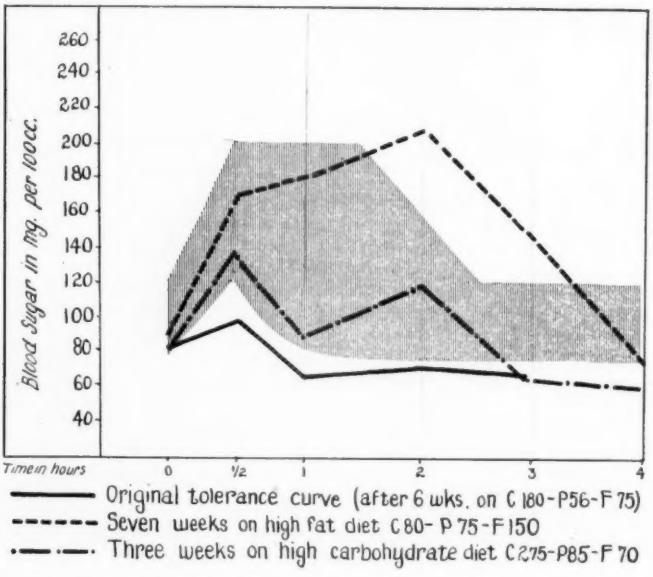

FIG. 2.—Tolerance decreased by low carbohydrate diet and increased by high carbohydrate diet.

the following levels in mg. per 100 cc.: 68, 140, 156, 141, 88, 45. A distinct hypoglycemic reaction occurred about the fourth hour.

On September 9, 1935, a cholecystectomy was done. The pathologic report showed chronic cholecystitis without stones. The clinical symptoms of weakness and perspiration persisted after operation and on September 21 she was given a weighed diet of C. 80, P. 75, F. 150, Cal. 1970. This was followed carefully while the patient was in the hospital and no more hypoglycemic reactions occurred. A glucose tolerance curve 7 weeks later showed a definite reduction in tolerance with a glycosuria of 0.63 gm. The fasting blood cholesterol level at this time was 272 mg. per 100 cc.

On January 4, 1936, a high carbohydrate diet (C. 275, P. 85, F. 70, Cal. 2070) was prescribed as a clinical test. At first the patient felt more energetic and had a better appetite. After 3 weeks a glucose tolerance curve showed a marked increase again in tolerance with no glycosuria. It is an interesting observation that the blood cholesterol level at this time had fallen to 208 mg. per 100 cc.

CASE 3.—The patient, a girl of 14, had generalized convulsions. A glucose tolerance test showed the following levels in mg. per 100 cc.; 81, 107, 82, 75, 79, 65.

The patient was given a diet high in fat, relatively low in carbohydrate (C. 110, P. 75, F. 160, Cal. 2180). Six weeks later the tolerance curve was as follows: 85, 114, 171, 122, 107, and 107 mg. per 100 cc. of blood. Four months after beginning the diet she was still free from convulsive seizures and at this time her glucose tolerance curve showed some further decrease in tolerance. The levels were 88, 155, 161, 124, 115, 115 mg. per 100 cc.

CASE 4.—A man of 47 complained of insomnia and periods of nervousness, associated with emotional instability, trembling, sweating, and groping for words. Two recent "faint" spells had been relieved by eating chocolate. He had lost approximately 35 pounds during the year. Physical examination failed to reveal any cause for his symptoms.

A glucose tolerance test showed increased tolerance with a hypoglycemic level at the third hour. It was as follows: 81, 113, 72, 85, 58, 73 mg. per 100 cc. of blood. He was given a diet of C. 110, P. 73, F. 117, Cal. 1785, which was increased 8 days later to C. 125, P. 88, F. 161, Cal. 2300. One month after the original glucose tolerance, a second test was as follows: 94, 154, 134, 103, 54, 72 mg. per 100 cc. It showed considerable reduction of tolerance; hypoglycemia, however, still persisted at the third hour. The patient was entirely relieved of his symptoms.

CASE 5.—A woman of 25 had begun to have convulsive seizures of grand mal type at the age of 16. These had become increasingly more frequent. Physical examination revealed no cause.

On February 5, 1936, a glucose tolerance test showed the following levels in mg. per 100 cc. of blood: 68, 106, 102, 105, 74, 69. She was given a diet low in carbohydrate (C. 100, P. 65, F. 120, Cal. 1740) with frequent feedings. Two months later the fat content was raised to 153 gm. (Cal. 2040).

Three months on this regimen resulted in a reduced tolerance. The blood sugar levels were as follows: 87, 127, 161, 139, 80, 60 mg. per 100 cc. The urine contained a trace of sugar and acetone. Clinically, there had been no improvement, two additional attacks having occurred.

CASE 6.—A woman of 20 complained chiefly of weakness, headaches, and dizziness. The symptoms were never related definitely to meals but could be relieved by a glass of sherry. She was short, slightly obese, the uterus was small, and pubic hair was scant.

The glucose tolerance was markedly increased with levels of 78, 98, 83, 61, 69, 48 mg. per 100 cc. of blood. She was given a diet of C. 72.5, P. 55, F. 122, Cal. 1608. Ten weeks later, considerable reduction of tolerance was noted

except at the fourth hour which fell to the hypoglycemic level of 53 mg. and the patient experienced typical symptoms of hypoglycemia. The sugar levels were as follows: 93, 142, 116, 116, 109, 53 mg. per 100 cc. She had made definite clinical improvement.

CASE 7.—A man of 29 had had attacks of weakness, nervousness, trembling, and at times hyperhydrosis for the preceding 9 years. He also suffered from insomnia, frequent headaches, and a constant tendency to stutter. Physical examination gave essentially negative findings. Five estimations of the basal metabolic rate over a 3½-year period gave normal findings.

A glucose tolerance test showed a markedly increased tolerance, the highest level being the fasting sugar. The values were 89, 88, 79, 54, 49, 70 mg. per 100 cc. of blood.

For 4 years he followed a low carbohydrate, high fat diet which was finally standardized to contain C. 100, P. 80, F. 200, Cal. 2520, taking 6 feedings per day. After 1 month and also 2½ months on this weighed diet, glucose tolerance tests were normal and exhibited considerable decrease in tolerance from the original curve. The levels after 2½ months on the above diet were 98, 169, 140, 69, 80, 88 mg. per 100 cc.

Three months later he was symptom-free but, for the purpose of investigation and with the patient's coöperation, his diet was radically changed to C. 275, P. 86, F. 95, Cal. 2300. Within 3 weeks the symptoms previously experienced were returning and 1 month after institution of this high carbohydrate diet, the tolerance test showed a definite increase in tolerance. The blood sugar levels were 117, 136, 82, 82, 70, 80 mg. per 100 cc. A high fat, lower carbohydrate diet was restored and soon he became free of symptoms once more. Symptoms may be reproduced at will by increasing the carbohydrate intake.

Group 2. CASE 8.—A woman of 38 complained of a burning, constant pain, variable in intensity, over the precordial region of the 4th and 5th interspaces. This had been present for almost 3 years. She also complained of great nervousness and weakness. Her history suggested hysteria. Her mother died of diabetes at the age of 65.

Examination revealed slight thyroid enlargement and an area of tenderness over the left anterior chest wall corresponding to the site of the pain. She was believed to have intercostal neuralgia as well as diabetes mellitus.

The glucose tolerance test showed a mild diabetic type of curve with 1.5 gm.—total glycosuria. The levels were 82, 208, 256, 173, 141, 93 mg. per 100 cc. of blood. She was given a high carbohydrate, low fat diet, consisting of C. 250, P. 80, F. 60, Cal. 1860.

A glucose tolerance test made 10 days later showed a definite increase in tolerance although there was 2.58 gm. of glycosuria. The sugar levels were 94, 173, 191, 184, 120, 64 mg. per 100 cc. After the diet had been continued 2 months longer, the glucose tolerance test was normal and no glycosuria was present. The levels were 81, 110, 127, 94, 111, 68 mg. per 100 cc. She felt well at this time except for the chest pain.

CASE 9.—A man of 59 had been found to have diabetes mellitus during a routine physical examination 3 years previously. Since then he had followed a modified low carbohydrate, high fat diet, approximating C. 120, P. 130, F. 120, Cal. 2080, and had been well controlled. Our glucose tolerance test indicated definite diabetes mellitus, with a glycosuria of 2.2 gm. The blood sugar levels were 120, 241, 297, 330, 214, 114 mg. per 100 cc.

He was in the hospital for 6 days for diabetic management. A diet of C. 190, P. 68, F. 100, Cal. 1932 was prescribed. No insulin was required, as diabetic control was complete.

The diet was gradually raised to C. 245, P. 93, F. 96, Cal. 2216 and the patient remained well controlled. This was repeated 20 months after the

original tolerance test. He had followed the diet containing C. 245 for 12 months prior to this time. The test, though retaining a suggestion of lagging, was now normal, with levels of 102, 160, 160, 187, 96, 62 mg. per 100 cc. The urine showed a very faint trace of glucose but this was too small to estimate quantitatively.

CASE 10.—A woman of 47 gave a history of chronic alcoholism of many years' duration. "All her life" she had suffered from "night-blindness." During the 18 months preceding admission she noticed increasing stiffness of the legs with uncertainty of gait. Her diet had been poor for 4 years and was entirely inadequate in meat and fruit. On examination, her skin was dry and rough. Her tongue was clean, red, and atrophic. Many crowned teeth were present. Hyperesthesia of the feet and legs and increased patellar reflexes were noted. The diagnoses were deficiency disease with peripheral neuritis, secondary to chronic alcoholism and diabetes mellitus.

She was given a high vitamin, high caloric diet with hydrochloric acid, brewer's yeast, haliver oil, and daily intramuscular injections of liver extract. During the next 2 weeks she ate poorly, due to poor appetite and because of the extraction of several teeth. Two weeks after admission a glucose tolerance test was made which showed a diabetic type curve with glycosuria of 0.3 gm. The levels were 110, 260, 288, 213, 160, 102 mg. per 100 cc. of blood. Three weeks after admission a weighed diet of C. 175, P. 65, F. 80, Cal. 1680 was prescribed and altered during the next 3 days to C. 205, P. 71, F. 80, Cal. 1824. After 2 weeks on this diet the tolerance test was entirely normal except for a faint trace of glycosuria. The sugar levels fasting and at 1, 2 and 3 hours were 83, 187, 133, 104, mg. per 100 cc.

In this case, several factors are present which modify the diagnosis of diabetes. In the first place she had existed on a very inadequate, almost starvation, diet prior to the time she entered the hospital, which was 2 weeks before the first glucose test. There were also distinct signs of deficiency disease and dental infection. Starvation diets, like diets low in carbohydrate and high in fat, cause a definite decrease in sugar tolerance.[7]

CASE 11.—A man of 48 complained of drowsiness, fatigue, coldness, poor memory, dry skin, somnolence, and gradual weight gain of about 80 pounds during the past 20 years. He stated that his appetite was large. Examination showed only moderate obesity and the skin signs suggestive of hypothyroidism.

Urinalysis showed 3+ sugar. A glucose tolerance test was done which revealed a mild diabetic curve and glycosuria of 2.9 gm. The levels were 82, 192, 222, 226, 140, 75 mg. per 100 cc. of blood.

A diet of C. 205, P. 71, F. 80, Cal. 1824 was prescribed and ½ gr. of desiccated thyroid daily. After 7 weeks on this regimen, the glucose tolerance test was normal, he had lost 20 pounds in weight, and the symptoms were greatly diminished. The blood sugar levels were 94, 171, 170, 105, 84, 73 mg. per 100 cc.

CASE 12 (Fig. 3).—A man of 50 was admitted for orthopedic care. Mild diabetes had been recognized 3 years before and he had limited the starch and sugar in his diet. Examination revealed that he was about 15 pounds overweight.

A glucose tolerance test showed a mild diabetic type of curve with a faint trace of glycosuria. He was given a diet low in fat and moderately high in carbohydrate which was gradually increased to C. 265, P. 83, F. 60, Cal. 1932. At first, glycosuria was noticed but this disappeared. After 1 month on this diet, a tolerance test showed definite increase in tolerance and was normal except for slight elevation at the third hour and a trace of glycosuria, insufficient for quantitative estimation.

The diet was then changed to one high in fat, low in carbohydrate, but of the same caloric value, consisting of C. 85, P. 70, F. 145, Cal. 1925.

After a month on this regimen the glucose tolerance test revealed a definite loss in tolerance at all periods up to the third hour.

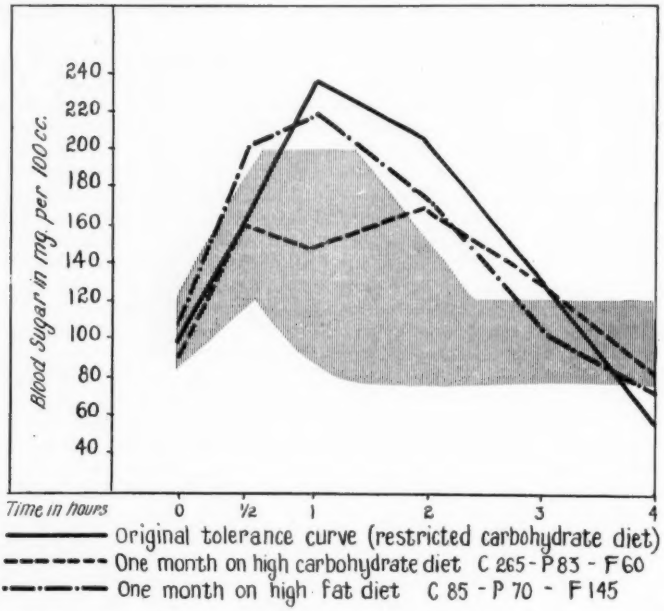

FIG. 3.—Decreased tolerance on low carbohydrate diet and increased on high carbohydrate intake in a diabetic.

Summary. The glucose tolerance test has been used to demonstrate the change in tolerance which occurs following the use of various diets.

Two groups of cases are presented: One, a group of 7 individuals with chronic hypoglycemia; and the other, a group of 5 patients classed as mild diabetes mellitus.

In the cases of chronic hypoglycemia, there was a consistent decrease in tolerance following the use of low carbohydrate, high fat diets. Subsequently, in 2 of these cases increased tolerance followed the use of high carbohydrate, low fat diets.

In the cases of mild diabetes mellitus the tests showed an increased tolerance following the use of high carbohydrate, low fat diets. In 2 cases, the original diminished tolerance shown in our data followed the use of restricted carbohydrate intake for several years. In 1 of these the tolerance gained following the use of a high carbohydrate intake was largely lost 1 month after the institution of a low carbohydrate diet of equal caloric value.

Since tolerance of glucose is altered so definitely by various diets, a knowledge of dietary habits is necessary for proper clinical evaluation of the glucose tolerance test.

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DIETARY VERSUS INSULIN TREATMENT OF THE OBESE DIABETIC PATIENT.*

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The principle of undernutrition in the treatment of diabetes, announced by Allen in 1914, was regarded as so important before the discovery of insulin that the years 1914–1921 are referred to as the Allen era. However, since the introduction of insulin in 1921, the undernutrition principle has not received the attention that it deserves, especially as applied to the treatment of obese diabetic patients. The importance of this neglect may be realized when it is known that the majority of diabetic patients are overweight. In most of the clinics for the treatment of diabetes that we have observed, overweight diabetic patients with high blood sugar levels are usually not reduced, but are placed on diets that maintain their weights. Insulin must then of necessity be given, and, with the patient's weight kept at a high level, large doses are necessary.

Text-books do not bring out the fact that reduction in weight of obese diabetics will, in a large majority of cases, improve the tolerance for carbohydrate and total calories and reduce the level of the blood sugar to normal without insulin therapy. For example, Joslin appears to regard the amount of glycosuria as the criterion for giving insulin, regardless of the patient's weight. In the last edition of his book, this author[3a] says that he would give protamine insulin, 10 units before breakfast, to a previously untreated diabetic whose urine shows a red or yellow reduction with Benedict's reagent. Grafe apparently believes that the height of the blood sugar alone indicates the need for insulin in an uncomplicated diabetic, again

* Read at the Section on General Medicine of the College of Physicians of Philadelphia, October 25, 1937.

regardless of the patient's weight. In his book on metabolic diseases, Grafe[2] states that: "If a (blood sugar) value of 0.3% or more is found, we may be sure that dietary restrictions alone will not suffice. The same is true if in spite of treatment a second analysis reveals a figure of about 0.2% without simultaneous renal or vascular disease. In such cases we are also dealing with the severe form of the disease which requires insulin."

As has been pointed out by Duncan[1] diabetes is mild in any patient if that patient has never taken insulin and is considerably overweight, regardless of the initial blood sugar level. Guided by this principle, we have customarily given a low-caloric diet to uncomplicated overweight diabetic patients, so as to reduce the weight gradually (not more than 2 pounds a week), to somewhere near the calculated ideal weight for the patient's age, sex and height. With the weight reduction and simultaneous reduction of the total metabolism, the apparent need for insulin disappears. *These statements must not be taken to mean that we do not give insulin when it is needed.* All of our more severe diabetic patients (who are usually underweight) and the mild diabetics when complications develop are, of course, given insulin. However, the percentage of our diabetic patients taking insulin is relatively low. Joslin[3b] has estimated that 60% of the diabetics in this country are now taking insulin. In the Diabetic Clinic "B" at Pennsylvania Hospital, of 112 patients now active in the clinic only 33% (a little more than half of Joslin's estimated figure) take insulin. Some of these are recovering from complications and will not be permanent "insulin patients." Recent figures show that only 25% require insulin treatment permanently.

It should be emphasized that the group of patients under discussion is a large one. The percentage of diabetic patients who are obese is astonishingly high. Joslin[3c] found that of 4596 diabetics over 20 years, 78.5% of the men and 83.8% of the women were overweight at their maximum weights, and the percentages overweight at the onset of the diabetes were almost as high. No less than 16.5% of the men and 25.8% of the women were 40% or more overweight at their maximum weights. These percentages are about what we have found in our clinic. It is with these very obese patients, 40% or more overweight, that we are particularly concerned in this discussion. The advantages of treating this large group of diabetic patients without insulin are obvious. Not the least of these is the financial saving to the patient, or to the hospital if it provides insulin when the patient cannot pay for it.

The cases to be reported were all treated in the out-patient department where we had to rely on the patients' coöperation in following the prescribed diets. It is worth noting here that it is particularly important to restrict the large calorie carrier, fat, as well as, or in place of, carbohydrate. In general, too little attention is paid to the advantages of this restriction and its effect in reducing the blood sugar level. When the patient coöperated in following his diet,

we found that the blood sugar level fell with the weight. If the patient refused to follow a low-caloric diet and maintained his high weight level, the blood sugar stayed high. To some of these patients we gave insulin, and found often that large doses (50 to 100 units daily) were needed to bring the blood sugar down to a normal level.

Illustrative Cases. Examples of obese diabetic patients belonging to two different groups are herewith presented. These cases are typical of all of the patients in each group. To save space and avoid repetition, the data on only a few of the patients in each group are included.

Group I. *Obese diabetic patients who showed a fall of the blood sugar level to normal with weight reduction.*

Case 1.—A. Fe., Female, White, Aged 51, Height 61 Inches, Ideal Weight 135 Lbs., 39% Overweight.

Date.	Weight, lbs.	Diet. P.	C.	Calories.	Glycosuria.	Blood sugar,* mg. per 100 cc.
July 7, 1933	188	70	80	1100	2.1%	250
July 21	184	70	80	1100	0	177
July 28	181½	70	80	1100	0	144
August 11	179	70	80	1100	0	122
October 20	170	70	95	1300	0	115
January 26, 1934	167¼	70	85	1200	0	110
August 24	153	70	95	1300	v. ft. trace	113
March 8, 1935	148	70	105	1400	0	113
July 12	147	70	115	1600	0	110
October 9, 1936	157½	70	115	1600	0	110
December 10	156	70	140	1600	0	120
June 25, 1937	165	75	160	1800	0	113
August 13	161	75	160	1800	0	109

Summary. With a loss of weight of 9 pounds, the blood sugar level fell from 0.250% to normal. Subsequently, the carbohydrate tolerance was much improved. Even with an increase in weight of 14 pounds from the lowest level, the blood sugar stayed normal.

Case 2.—D. d'G., Female, White, Aged 46, Height 59¼ Inches, Ideal Weight 126 Lbs., 49% Overweight.

Date.	Weight, lbs.	Diet. P.	C.	Calories.	Glycosuria.	Blood sugar,* mg. per 100 cc.
March 25, 1932	186	70	80	1100	1.3%	238
April 1	178½	70	80	1100	0	152
April 15	174	70	80	1100	0	130
April 29	173½	70	80	1100	v. ft. trace	99
May 13	167	70	80	1300	0	88
July 8	155¼	70	80	1300	0	93
December 16	153½	70	120	1700	0	77
April 7, 1933	151	70	150	1700	0	76

Subsequently the carbohydrate in the patient's diet was increased to 250 gm. daily, the calories being kept at 1700. There was a gradual gain of weight to 174 pounds on August 13, 1937 (evidently the patient was exceeding her caloric allowance). The glucose tolerance test on January 27, 1936 showed a mildly diabetic curve, the highest blood sugar being 0.199% 1 hour after the administration of 100 gm. of glucose.

Summary. With a loss of weight of 9 pounds the blood sugar level fell from 0.238% to normal. Subsequently, even with an increase in weight of 21 pounds from the lowest level, the blood sugar stayed normal, showing a marked increase in the carbohydrate tolerance.

* All blood sugar determinations were made by the Folin-Wu method. The blood specimens were taken from patients who had fasted at least 14 hours.

CASE 3.—F. H., FEMALE, COLORED, AGED 35, HEIGHT 60½ INCHES, IDEAL WEIGHT 124 LBS., 27% OVERWEIGHT.

Date.	Weight, lbs.	Diet. P.	C.	Calories.	Glycosuria.	Blood sugar,* mg. per 100 cc.
May 8, 1936	157	70	90	1200	1.6%	258
May 15	155	70	90	1200	0	192
June 5	152½	70	90	1200	0	169
July 24	147	70	90	1200	0	141
September 4	145	70	90	1200	0	111
November 6	143	70	90	1200	0	130
March 5, 1937	135	70	125	1400	0	134
April 16	137	70	125	1400	0	143
July 9	138	70	125	1400	0	161
September 3	139	70	125	1400	0	119

Summary. With a loss of weight of 10 pounds, the blood sugar level fell from 0.258% to normal. Subsequently, with an increase in the caloric allowance the blood sugars were slightly higher, but usually near the normal level.

CASE 4.—L. G., FEMALE, WHITE, AGED 62, HEIGHT 61½ INCHES, IDEAL WEIGHT 140 LBS., 37% OVERWEIGHT.

Date.	Weight, lbs.	Diet. P.	C.	Calories.	Glycosuria.	Blood sugar,* mg. per 100 cc.
February 19, 1934	192½	70	80	1200	Not done	238
March 23	188½	70	80	1200	0	170
April 13	185	70	80	1200	0	178
May 25	178¼	70	80	1200	0	143
August 3	168	70	80	1200	0	156
November 9	169	70	80	1200	0	137
January 16, 1935	162½	70	100	1200	0	126
April 12	165	70	100	1200	0	114
September 13	171	70	100	1200	0	122
January 10, 1936	174	70	100	1200	0	125
May 1	173	70	100	1200	0	114
November 13	174	70	100	1200	0	126
January 15, 1937	177	70	100	1200	0	133
June 25	174	70	100	1200	0	137

Summary. With a loss of weight of 25 pounds, the blood sugar level fell from 0.238% to nearly normal. Subsequently, with a slight increase in weight (apparently the patient was exceeding her caloric allowance) the blood sugar did not exceed 0.137%.

CASE 5.—A. FR., FEMALE,, WHITE, AGED 48, HEIGHT 63 INCHES, IDEAL WEIGHT 140 LBS., 46% OVERWEIGHT.

Date.	Weight, lbs.	Diet. P.	C.	Calories.	Glycosuria.	Blood sugar,* mg. per 100 cc.
August 13, 1934	205	80	90	1400	0.8%	225
August 24	207	72	90	1200	Ft. positive	185
September 7	203	80	85	1200	0	166
September 19	198	80	85	1200	0	169
October 12	195½	80	85	1200	0	151
December 7	189	80	85	1200	0	145
March 1, 1935	186	80	85	1200	0	132
April 12	185	80	85	1200	0	119
July 19	182½	80	85	1200	0	123
October 18	182¼	80	85	1200	0	103
March 20, 1936	184½	80	100	1200	0	118
July 10	184	80	100	1200	0	121
January 15, 1937	182	80	100	1200	0	115
April 16	183	80	100	1200	0	111

Summary. With a loss of weight of 20 pounds, the blood sugar level fell from 0.225% to normal. With no further loss of weight, the blood sugar has remained normal.

* All blood sugar determinations were made by the Folin-Wu method. The blood specimens were taken from patients who had fasted at least 14 hours.

CASE 6.—A. C., FEMALE, WHITE, AGED 59, HEIGHT 61 INCHES, IDEAL WEIGHT 133 LBS., 42% OVERWEIGHT.

Date.	Weight, lbs.	Diet. P.	Diet. C.	Diet. Calories.	Glycosuria.	Blood sugar,* mg. per 100 cc.
May 12, 1936	189½	65	100	1200	3 plus	220
May 23	188	65	100	1200	1 plus	140
June 6	186½	65	100	1200	0	147
June 20	181½	65	100	1200	0	97
August 1	173	65	100	1200	0	80
October 8	173	65	100	1200	0	115
February 4, 1937	171½	65	100	1200	0	100
April 1	176	65	100	1200	0	95
June 17	165¼	65	100	1200	0	95

Summary. With a loss of weight of 7 pounds, the blood sugar level fell from 0.220% to normal. With a continued gradual loss of weight, the blood sugar has remained normal.

Group II. *Obese diabetic patients who failed to follow a low-caloric diet, and therefore needed insulin.*

CASE 7.—M. M., FEMALE, WHITE, AGED 56, HEIGHT 63 INCHES, IDEAL WEIGHT 138 LBS., 46% OVERWEIGHT.

Date.	Weight, lbs.	Diet. P.	Diet. C.	Diet. Calories.	Insulin.	Glycosuria.	Blood sugar,* mg. per 100 cc.
April 18, 1936	201	60	120	1125	20—20—20	0	250
May 16	202½	60	120	1125	20—20—20	0	152
July 11	198½	60	120	1125	20—0—20	0	170
September 24	197½	60	120	1125	20—0—20	4 plus	300
November 5	197½	60	120	1125	(35)—0—(10)	4 plus	247
December 24	201	60	120	1125	(40)—0—(10)	4 plus	160
January 21, 1937	197½	60	120	1125	[40] —0— [10]	Not done	250
April 1	198	60	120	1125	[45] —0— [18]	4 plus	174
April 15	195	60	120	1125	[50] —0— [50]	4 plus	305
May 20	197	60	120	1125	[60] —0— [50]	4 plus	200
June 24	194	60	120	1125	[60] —0— [50]	4 plus	400

Note: ( ) represents protamine zinc insulin; [ ] represents crystalline insulin.

Summary. With failure of the patient to follow a low-caloric diet, the diabetes remained uncontrolled even with 110 units of crystalline insulin daily.

* All blood sugar determinations were made by the Folin-Wu method. The blood specimens were taken from patients who had fasted at least 14 hours.

CASE 8.—H. D., FEMALE, WHITE, AGED 43, HEIGHT 62 INCHES, IDEAL WEIGHT 133 LBS., 9% OVERWEIGHT.

Date.	Weight, lbs.	Diet.			Insulin.	Glycosuria.	Blood sugar,* mg. per 100 cc.
		P.	C.	Calories.			
July 3, 1934	144½	70	80	1200	None	1.6%	209
September 14	141½	70	80	1200	8—0—0	v. ft. trace	171
November 12	142	70	80	1100	11—0—0	0	166
January 7, 1935	145	70	80	1100	15—0—8	0	191
June 7	146	70	80	1100	12—0—10	0	254
October 14	153½	70	80	1100	11—0—10	0	159
January 6, 1936	156	70	80	1100	11—0—10	0	124
December 11	158	70	80	1100	8—0—12	0	235
January 22, 1937	158	70	80	1100	15—0—6	0	202
March 5	158	70	125	1400	(26)—0—0	0	141
May 21	163	70	125	1400	(45)—0—0	0	207
July 16	166	70	125	1400	(48)—0—0	0	191

Summary. With a weight gain of 22 pounds because of failure to follow a low-caloric diet, the insulin requirement rose steadily. Even with 48 units of protamine zinc insulin daily, the diabetes was not well controlled.

CASE 9.—E. P., FEMALE, WHITE, AGED 61, HEIGHT 62 INCHES, IDEAL WEIGHT 138 LBS., 6% OVERWEIGHT.

Date.	Weight, lbs.	Diet.			Insulin.	Glycosuria.	Blood sugar,* mg. per 100 cc.
		P.	C.	Calories.			
November 9, 1934	146	70	90	1400	None	1.3%	265
November 16	146	70	90	1200	None	1.2%	234
January 4, 1935	145	70	90	1200	None	0	209
April 5	147	70	90	1200	None	0	186
October 21	150½	70	90	1200	None	0	200
December 6	151	70	90	1200	None	0.4%	155
June 19, 1936	146½	70	90	1200	None	1 plus	267
July 10	144	70	100	1200	8—0—6	0	195
November 20	154	70	100	1200	9—0—7	0	165
April 16, 1937	155¼	70	100	1200	(12)—0—0	1.4%	212
June 18	155	70	100	1200	(12)—0—0	1 plus	227

Summary. With a weight gain of 10 pounds, because of failure to follow a low-caloric diet, the diabetes was uncontrolled with relatively small doses of protamine zinc insulin.

Summary and Conclusions. We have presented case histories of obese diabetic patients which illustrate the following facts:

The great majority of obese diabetic patients, particularly those 40% or more overweight, do not need insulin. When such a patient is put on a low-caloric diet and his weight reduced, the blood sugar

* All blood sugar determinations were made by the Folin-Wu method. The blood specimens were taken from patients who had fasted at least 14 hours.

falls to normal without insulin. If such a patient is put on a diet that maintains his weight, large doses of insulin are needed to control the diabetes. Obviously, if simple weight reduction can achieve the same results as large doses of insulin, it is the treatment of choice in obese diabetic patients, especially as the loss of weight is in itself a desirable end.

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THE EFFECT ON THE BLOOD CELLS OF THE FETAL RAT PRODUCED BY THE INHALATION OF CARBON TETRACHLORIDE BY THE MOTHER DURING GESTATION.*

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Studies on the blood of fetal mammals have shown that their total number of erythrocytes per cubic millimeter is very low and that the size and volume of the erythrocytes are much greater than corresponding values for the adult. During gestation the total number of cells per cubic centimeter gradually increases and the size and volume of the cells gradually decrease; but at birth these values are far from approaching the corresponding values for adult blood.[17,31]

Wintrobe and Shumacker[32] compared these changes during the development of fetal blood with changes which occur in the blood of patients with pernicious anemia who are receiving some potent stimulus to blood formation. They thought that there must be some hemopoietic principles or stimulus which likewise controls the maturation of the fetal blood cells. Nothing is known regarding the possible hemopoietic factors which may be elaborated by the fetus. Gastric motility and gastric secretion of the fetal stomach have been studied,[33] but whether these secretions contain either intrinsic or extrinsic factors for regulation of the blood remains unknown. Jones, Shipp and Gonder have said that, "perhaps the factor is absorbed from the mother or it may be elaborated by the fetus." Wintrobe and his associates suggested that if a substance similar to Castle's antianemic principle[28] does influence the blood of the fetus, it probably comes through the placenta from the maternal circulation.

There are some data[27b] which show that human gastric juice, or hog gastric juice obtained from a fundic pouch, when injected into

* Work done under the direction of Dr. G. M. Higgins.

pregnant rats, will accelerate the maturation of the fetal erythrocytes. This would seem to indicate that the antianemic principle found in gastric juice may pass through the placenta to the fetus. Wintrobe, Kinsey, Blout and Trager, on the other hand, failed to find any changes in the blood of fetal rabbits when they injected liver extract into the adult pregnant rabbit.

The occurrence of macrocytic anemia is evidence of the lack of adequate antianemic principle. If this principle be supplied, as in the administration of liver, then the macrocytosis disappears. If the fetus depends for its antianemic factor upon the mother, then a reduction in the maternal stores might manifest itself in changes in the fetal blood.

The inhalation of carbon tetrachloride by white rats will produce marked hepatic cirrhosis accompanied by a macrocytic anemia.[16,27a] After 3 weeks of inhaling the drug for brief periods daily the number of erythrocytes per c.mm. drops from an average of 9.18 millions to 7.52 millions, and the size of the erythrocytes increases from a normal of 6.09 microns to 7.16 microns. Although there are no direct data to support the conclusions, the macrocytosis in these rats which have inhaled carbon tetrachloride may be due to a reduction in the available antianemic principle supplied by the stomach.

This present report covers the results of a study made on the blood of new-born rats that were born of adults which had been forced to breathe the fumes of carbon tetrachloride for brief periods each day during the period of gestation.

Methods. Female rats of the Wistar strain were mated. Insemination was established microscopically by the presence of spermatozoa in the vaginal smears. A total of 60 inseminated rats then breathed the fumes of carbon tetrachloride for periods of from 30 to 60 minutes daily from the second day following insemination to parturition.

Of these 60 rats, 12 lived to term and bore 86 offspring, the blood of which was studied as soon after birth as possible. The data assembled from studies of the blood of these new-born rats included determinations of the total number of erythrocytes and leukocytes per c.mm. of blood; differential leukocyte counts, including the percentage of myelocytes, metamyelocytes and granulocytes; the volume of packed erythrocytes; determinations of hemoglobin; the number of normoblasts, reticulocytes and thrombocytes, and the diameters of the erythrocytes.

Samples of blood were taken from the new-born rats by cardiac puncture, standard pipets being used. Hayem's solution was used as a diluent for the erythrocytes, and a 3% solution of glacial acetic acid with the addition of cresylecht violet (1 to 10,000) after the method of Kindred and Corey,[19] was used as a diluent for the leukocytes.

Standard hematocrit tubes, with heparin as the anticoagulant, were used for hematocrit determinations. Hemoglobin was measured in grams per 100 cc. of blood by means of the photoelectric method. The differential leukocyte, normoblast and reticulocyte counts were made from dry smears stained by the May-Grünwald-Giesma technique. The blood for the reticulocyte counts was mixed with cresyl blue, smears prepared and stained. For both the normoblast and reticulocyte counts the percentage of cells per 1000 erythrocytes was determined. Thrombocytes were counted by means

of a micromethod in which the dilution of 0.1 cc. of blood was made in 1.9 cc. of a solution of sodium oxalate. Small vials were used as sedimentation tubes. The diameter of 100 erythrocytes for each of 15 animals was measured by projecting the cells of a dried smear with a camera lucida on to a micron scale at a magnification of 3000 diameters. The mean corpuscular volume, mean corpuscular hemoglobin, and the mean corpuscular concentration of hemoglobin were computed by the method of Wintrobe.

The number of erythrocytes per cubic millimeter of blood of the mother of each litter at parturition was also determined. Blood of the adult was taken from the ear vein, standard pipets being used.

Results. During the 3 weeks these pregnant rats breathed the fumes of carbon tetrachloride a definite anemia developed. The average erythrocyte count for the 12 rats (7.84 ± 0.15 millions) was very close to the figure of Higgins and Stasney (7.52 ± 0.15)[16] after treating normal male rats for 3 weeks.

TABLE 1.—COMPARISON OF DATA ON THE BLOOD OF NORMAL NEW-BORN RATS AND THOSE BORN OF MOTHERS SUBJECTED TO THE FUMES OF TETRACHLORIDE.

Stage.		Hematocrit, vol. %.	Hemoglobin, gm. per 100 cc.	Reticulocytes, % of total erythrocytes.	Thrombocytes, thousands per c.mm.	Normoblasts, per 1000 erythrocytes.	Erythrocytes, millions per c.mm.	Leukocytes, thousands per c.mm.
Normal	Number of animals	15	15	15	15	15	15	15
	Mean	47.3 ±5.5	26.9 ±0.24	94.2 ±0.5	427.9 ±17.0	0.313 ±0.20	3.27 ±0.32	3.22 ±0.13
	Standard deviation	31.8	1.4	3.2	98.8	1.17	1.84	0.76
	Coefficient of variation, %	67.3	5.2	3.4	22.8	373.8	56.6	23.6
After subjection of mother to fumes of CCl_4	Number of animals	15	15	15	15	15	20	20
	Mean	38.8 ±4.69	28.9 ±1.5	97.5 ±2.5	562.4 ±13.4	0.32 ±0.19	2.45 ±0.05	6.23 ±2.72
	Standard deviation	8.1	0.2	0.4	23.4	0.13	0.41	2.12
	Coefficient of variation, %	12.06	5.5	2.5	23.9	353.1	1.65	34.1

TABLE 2.—PERCENTAGE DISTRIBUTION OF CELLS IN THE BLOOD OF NORMAL NEW-BORN RATS AND THOSE BORN OF MOTHERS SUBJECTED TO THE FUMES OF CARBON TETRACHLORIDE.

Stage.		Myelocytes.	Metamyelocytes.	Granulocytes.	Lymphocytes.
Normal	Number of animals	25	25	25	25
	Mean	23.0 ± 1.3	47.7 ± 2.2	16.7 ± 1.4	13.8 ± 1.1
	Standard deviation	9.8	16.0	10.7	8.0
	Coefficient of variation	42.7	33.6	64.3	57.8
After subjection of mother to fumes of CCl_4	Number of animals	25	25	25	25
	Mean	34.3 ± 2.4	44.3 ± 1.0	11.3 ± 1.0	11.9 ± 1.1
	Standard deviation	17.6	7.13	7.2	8.2
	Coefficient of variation	51.2	16.1	64.1	68.5

TABLE 3.—COMPARISON OF SIZE OF ERYTHROCYTES.

Stage.	No. of cells measured.	Greatest diameter.			Least diameter.			Average diameter.		
		Microns.		C.V. %.	Microns.		C.V. %.	Microns.		C.V. %.
		Mean.	S.D.		Mean.	S.D.		Mean.	S.D.	
Normal	2100	9.24 ±0.05	3.8	40.7	8.60	3.7	42.6	8.80	1.2	13.0
After subjection of mother to fumes of CCl_4	1500	9.60 ±0.03	1.6	17.0	8.85 ±0.02	1.2	14.0	9.01 ±0.06	3.3	36.9

S.D. = standard deviation. C.V. = coefficient of variation.

TABLE 4.—CHANGES IN THE DIAMETER, VOLUME AND HEMOGLOBIN CONTENT OF ERYTHROCYTES IN EXPERIMENTAL MACROCYTIC ANEMIA.

Stage.	Mean cell diameter, microns.	Mean corpuscular volume, cubic microns.*	Mean corpuscular hemoglobin, micro-micrograms.*	Mean corpuscular concentration of hemoglobin, %.*
Normal	9.24 ± 0.05	145.5	8.2	5.7
Anemia	9.60 ± 0.03	158.3	11.8	71.0

* Computed by the method of Wintrobe (1932).

The data derived from the blood of rats born of these 12 mothers, together with the data[5] assembled from new-born rats of mothers not treated with carbon tetrachloride are condensed in the accompanying tables (Tables 1–4). Most significant, perhaps, was the decrease in the number of erythrocytes per c.mm. and the decrease in the hematocrit reading (Table 1) from the normal levels. Coupled with the decrease in the number of erythrocytes there was an increase in the diameters of the erythrocytes and in their volumes (Table 4). There was an increase in the hemoglobin content of the erythrocytes and in the number of reticulocytes, normoblasts, leukocytes and thrombocytes (Table 1). There was a shift to the left in the cells of the myeloid line, and an increase in the number of immature cells in the circulating blood (Table 2).

When the percentage frequencies of the erythrocyte diameters were plotted (Fig. 1), the curve depicting the distribution of erythrocytes in rats born of mothers treated with carbon tetrachloride indicated the extent of macrocytosis induced in the fetus.

Comment. The effect on the erythrocytes in the blood of the developing fetus produced by the inhalation of carbon tetrachloride by the mother are comparable to changes which occur in the maternal blood. Normal maturation of the fetal blood was inhibited or greatly retarded, so that rats were born with values for erythrocytes that were characteristic of a late-term fetus rather than of a newborn rat.

Two possible explanations of the results of this study, in which macrocytic anemia was induced in new-born rats, need to be considered: Is the fetal anemia the direct result of the action of the drug upon the fetus, or is it due to a reduction in the maternal stores of the antianemic principle, thereby restricting the amounts made available to the fetus? Placental transmission of the drug is of course a probability, numerous reports[8,12,20,24,25] of the transfer of various substances across the placental barrier having been made. Studies on the transfer of such gases as oxygen and carbon dioxide across the placenta have been reported, and disassociation curves have been established;[1,4,9,10,13,18,22,23] but I know of no data on such transfer of carbon tetrachloride. It seems likely, however, that this gas may likewise enter the fetal blood stream.

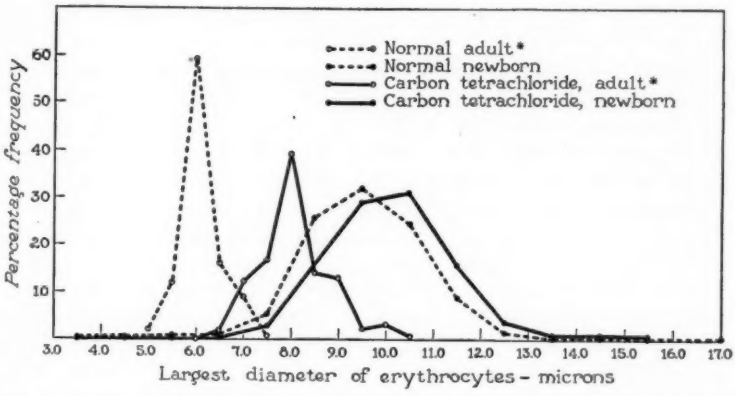

FIG. 1.—Curve of changes in percentage distribution of erythrocytes, according to size, in adult and new-born rats treated with CCl_4.

Since carbon tetrachloride is toxic and known to produce extensive changes in adult tissue other than hepatic cirrhosis and anemia, one should expect to find far-reaching changes in the tissues of the fetus if the drug had entered the fetal blood stream. Although unfortunately microscopic studies were not and cannot now be made, there was never any evidence of gross damage. The rats born of mothers which had received carbon tetrachloride were usually in good condition and there was no evidence of hepatic cirrhosis, hepatic damage being readily detectable even after very slight contact with carbon tetrachloride.

If the drug had caused the changes in the blood of the fetus, then one must postulate that the fetus elaborates the antianemic principle. No one thus far has shown that the fetus does elaborate its own antianemic principle. The extracts made of fetal livers, when injected, have not given consistent results. Goldhamer, Isaacs and Sturgis[11] reported a reticulocytosis of 17.6% when they gave human

fetal liver, and Berglund reported a slight response to fetal calf livers. Wintrobe, however, could detect no response to fetal pig liver in patients who were suffering from pernicious anemia and who were in relapse. Nothing is known of the relation of the fetal stomach to hemopoiesis. It is not likely that the drug acted directly on the hemopoietic centers to destroy them. Higgins and Stasney observed a hyperplastic bone marrow, rather than an aplastic one, in animals receiving the drug daily.

It seems more probable that the effects induced in the fetus are the result of changes set up in the elaboration and storage of the antianemic factors in the mother. How carbon tetrachloride affects or reduces the principle in the adult rat is not clear, but it seems in some way associated with the degree of hepatic damage. The greater the hepatic damage the greater the degree of anemia. Sturgis,[29] in 1935, expressed the belief that the intrinsic factor normally produced by the stomach and stored in the liver was not available to the organism with a damaged liver because of its restricted storage capacity. These same conclusions were reached by Shumacker and Wintrobe.[26] Goldhamer, Isaacs and Sturgis[11] showed that extracts of a human cirrhotic liver elicited no reticulocyte response when given to a patient with pernicious anemia. Gastrectomy in the rat produced a hypochromic microcytic anemia[2] instead of a macrocytosis; but it may be that the intrinsic factor of Castle[28] is elaborated elsewhere in the intestines of rats as well as in the stomach. Carbon tetrachloride invariably upsets the gastro-intestinal tract of animals. Peristalsis is inhibited and food may remain in the stomach for days. It is possible that the drug restricts the elaboration of the intrinsic factor in the stomach, thus accounting for the macrocytosis which ensues. It is known, experimentally, that the factor present in human or hog gastric juice does pass the placental barrier and will affect the developing blood cells in the fetus.[2,27b] Thus there is reason to believe that, normally, this same transfer occurs and that the fetus depends for its hemopoietic stimulus upon the mother.

The high level of hemoglobin (Table 1) which was present in these rats may perhaps be accounted for by the hypothesis formulated by Whipple[30] and Heath[14] in their analysis of the hemoglobin content of the red corpuscle. They assumed that in pernicious (macrocytic) anemia, a deficiency in the stroma-building substance occurs, that all maturation is inhibited although hemoglobin formation takes place in a normal manner and, therefore, that the few cells which are being manufactured are saturated with hemoglobin and are in most cases enlarged in order to carry as much hemoglobin as possible.

The marked variation in the size of the erythrocytes (Fig. 1) agrees with the observation of Henry,[15] who also observed a difference in the size of the cells and the presence of a number of large ones, in his study of anemia in the new-born infant. The results

of the present study (Fig. 1) showed the degree of macrocytosis and the range in diameters which have been produced in both the adult[16] and in the new-born rat following inhalation of the fumes of carbon tetrachloride.

The increase in the more immature cells noted in the differential leukocyte counts (Table 2) is similar to that observed by Klenerman,[21] who described a shift to the left (Arneth) in her study of the blood of infants. Brown, Morrison and Meyer[6] observed a leukocytosis, also with the shift to the left, in their studies of anemia in new-born infants.

Summary. Pregnant female white rats were rendered anemic by inhalation of the fumes of carbon tetrachloride. A cytologic study of the blood of the 86 rats born of these anemic mothers that had breathed carbon tetrachloride during gestation was then made and the results were compared with those of a study of the blood of 72 rats born of untreated mothers.

Macrocytic anemia developed in the fetus during intra-uterine development. This was evidenced particularly by a decrease in the number of erythrocytes per c.mm. of blood and by an increase in the diameters and mean corpuscular volumes of the erythrocytes. Other changes which have been observed include an increased hemoglobin content, reticulocytosis, thrombocytosis, leukocytosis, and a shift to the left (Arneth) in the differential leukocyte count.

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THE EFFECT OF IONTOPHORESIS WITH ACETYL-BETA-METHYLCHOLINE CHLORIDE ON THE RATE OF PERIPHERAL BLOOD FLOW.

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Although acetyl choline has long been known to be an extremely powerful vasodilator, its therapeutic usefulness for this purpose is limited by the dual nature ("nicotinic," "muscarinic") of its actions, by its great instability, and by the variety of other effects produced by it in addition to the desired vasodilation. Acetyl-β-methylcholine ("Mecholyl") is free of the first of these limitations because it is devoid of nicotinic actions, and less subject to the second because it is more stable than acetyl choline. It is, however, just as objectionable as acetyl choline from the standpoint of undesired effects (salivation, sweating, increased peristalsis, bronchial constriction, etc.) when the drug is absorbed into the circulation, and its therapeutic value as a vasodilator in peripheral vascular disease is correspondingly compromised. Kovacs and Kovacs[6a,b,7a,b,8,13] and Rutenbeck[12] have demonstrated that choline derivatives can be driven through the skin by means of an electric current (iontophoresis) and have opened the way for local therapy by these compounds.

Acetyl-β-methylcholine chloride, hereinafter termed ABMC, has had the widest use in this connection. The results point to the value of ABMC iontophoresis in treating some peripheral arterial disorders and arthritides, long-standing varicose ulcers,[13] scleroderma,[2] and thrombophlebitis.[10] The implication is that the clinical improvement results from increased blood flow produced locally in the part of the body that is treated; but as far as we are aware no direct evidence has been adduced as to the extent of such increase or even as to its actual occurrence. J. Kovacs[6a] reported an increase of 4° to 10° F. in the temperature of the limb treated, but the conditions under which these measurements were made are not clearly stated. If they took place after removal of the treating electrode, the rise in temperature might have represented only the influence of removal of the cooling effect of the solution with which

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the electrode was saturated. Or, later rises in skin temperature might have represented the removal of the cooling effect of sweating caused by the drug. Cohn and Benson[1] used a technique which minimized evaporation and found an increase in skin temperature that did not exceed 1° C. Evidence that vasodilation occurs is found in increased oscillometric readings following ABMC iontophoresis, in erythema and in an increase in capillary flow at the site of application,[7b] but blood flow measurements and information in respect to a local *versus* a systemic increase in blood flow are lacking. One of the advantages of iontophoresis over other methods of administering ABMC is that by it one may elicit considerable local vasodilation where it is therapeutically needed without producing disadvantageous systemic actions, but the effect should involve the major part of the vascular bed of the treated part. On the other hand, if iontophoresis should merely produce slight but relatively prolonged systemic choline effect, no greater in the treated part than elsewhere, this method would have no advantage over other less cumbersome ones.

The object of the present investigation was to determine, by direct measurement, the effect of ABMC iontophoresis on blood flow in the limbs of normal individuals. A few corresponding observations have also been made on patients with peripheral vascular disease. A number of experiments were also made on dogs, but the results of these differ in some respects from those obtained in man, and so will be mentioned only briefly.

Method. To estimate the volume of blood flowing through a limb in a human subject we measured plethysmographically the rate at which limb volume increased when venous outflow was momentarily obstructed. Two hand plethysmographs of similar design were used. They are modifications by Freeman[3] of the instrument described by Hewlett and Van Zwaluwenburg.[4] Since they are made of metal it was possible to utilize the entire plethysmograph as the positive electrode for iontophoresis and thus to measure blood flow before, during, and after the treatment without altering the conditions of the experiment in any way. Since the experience of others (confirmed in our experiments on dogs) shows that direct contact of a metal electrode with the skin during iontophoresis produces burns, we lined the plethysmographs with rubber sheeting, $\frac{1}{4}$ inch thick, provided with numerous $\frac{1}{4}$ inch holes, and the metal at the wrist end of the plethysmograph was replaced with bakelite. The procedures used to seal the plethysmograph and to obviate changes in temperature of the part were those described by Freeman.[3] The experiments were carried out in a room maintained at constant temperature by automatic control. Changes in limb volume were kymographically recorded by a Krogh spirometer. To occlude venous outflow a wrist cuff was inflated to a pressure just below the arterial diastolic level. Measurements were made at intervals of 5 to 10 minutes. The apparatus was calibrated by injecting known volumes of fluid into the plethysmograph, and the volume of the hand was estimated by displacement of water so as to permit us to report the figures for blood flow in terms of cc. per 100 cc. of hand per minute.

The source of current for iontophoresis consisted of a 45 volt "B" battery and was controlled by a 10,000 ohm variable resistance. A 60 milliampere

fuse was kept in the circuit. When two plethysmographs were used simultaneously separate ammeters and resistance units were used in each circuit. Current was turned on at about 4 milliamperes and gradually increased or decreased at a rate consistent with the comfort of the subject. Currents of 20 to 35 milliamperes were used for periods of 35 to 90 minutes. The negative electrode consisted of a sheet of copper screening 10 by 14 inches covered with several layers of gauze and one of light canvas. It was moistened with saline and applied to the back of the thorax. The plethysmograph was filled with 0.2% ABMC for iontophoresis, with tap water for control observations. To minimize the possible danger of escape into the subject of the 110 volt current used to operate the heating unit and stirrer of the plethysmograph, the latter was grounded, but this could not be done when two plethysmographs were used simultaneously.

Experiments were conducted on normal subjects and on patients in the same manner except that in the case of some of the normal subjects two plethysmographs, one on each hand, were used. The subjects were lightly clothed, with clothing adjusted in accordance with their comfort. The room temperature was kept constant during an experiment by automatic control, and the temperature of the fluid in the plethysmograph was kept nearly constant by a heater and a cooling jacket. Plethysmographic readings were taken at 5 to 10-minute intervals. The rate of blood flow fell during the pre-experimental period because of rest and because the room was somewhat cooler than the outside air. Controls were run in three different ways: (1) Blood flow was measured in only one hand using current but no ABMC; (2) blood flow was measured in both hands, with the drug and current on one hand and no current and no drug on the other; (3) blood flow was measured in both hands, with the drug and current on one and current but no drug on the other. When current was run through both hands the amount of current through each was made the same, and is reported in Table 1 as the amount in either hand, not as the amount at the source for the two leads.

The data to be presented were obtained on 6 healthy young adults and 3 young male patients with thromboangiitis obliterans and definite occlusive disease of the arteries of the hand. These patients had more severe obliterative changes in the feet than in the hands, but in each case there were sufficient changes in the hand to produce cold, blue fingers, decreased oscillations at the wrist, and a delayed filling of the hand as determined by an Allen test. B. G. (Table 1) had a thrombosed radial artery, as shown by surgical exploration. J. S. and B. G. had been sympathectomized in other limbs than those subjected to iontophoresis and to measurement of rate of blood flow. When the experiments were done none of the patients had open lesions on the hands.

Results. Iontophoresis through a plethysmograph containing 0.2% ABMC invariably caused a very marked increase in blood-flow in the treated hand (Table 1). As a rule the effect began after the current had been on for less than 15 minutes, reached a maximum within about 30 minutes, remained at that point as long as the current continued to flow, and began to decline almost as soon as the iontophoresis ceased. The duration of the increased blood flow after the current was turned off varied considerably, but as a rule recovery was practically complete within an hour (Table 1).* The patients with diseased arteries responded in the same general way

* The shortest duration was 30 minutes, the longest more than 105 minutes.

as the normal subjects although the increase in blood flow was somewhat less marked in the patients, as would be expected. Thus in the normal subjects the initial flows varied between 1 and 14 cc. (average 4 cc. per minute per 100 cc. of hand) and between 12 and 32 cc. at the height of the ABMC effect. In the patients with obliterative disease the initial flows varied between 1 and 14 cc., those at the height of the drug's effect between 12 and 24 cc. No increase in blood flow was ever observed in the untreated (control) hand. Current without the drug produced either a slight rise or no rise in blood flow through the control hand. The drug without current had no effect on blood flow. The results are shown in Table 1 and representative graphs in Figs. 1 and 2.

TABLE 1.—BLOOD FLOW IN THE HUMAN HAND UNDER ABMC IONTOPHORESIS.

Subject.*	Date, 1937.	Temperature (° C.).		Current.		Blood flow in hand (cc./100 cc. hand/min.).				
		Room.	Plethys.	mA.	Duration, min.	Initial.	Highest.	Recovery.		
								½ hr.	1 hr.	1½ hrs.
Normal, treated:										
C. F.	7/6	26	30.0 ± 0.3	20	35	1–2	12	1		
H. M.	7/8	26	28.5 ± 1.5	35	66	1	30	3	2	
C. F.	7/14	24	27.9 ± 1.3	30	40	2–11	25	18	16	17
C. F.	7/21	23	27.2 ± 0.7	30	40	2–4	26	7	7	4
H. P.	7/27	29	29.8 ± 0.3	30	46	7–14	19	19		
C. F.	7/29	26	30.1 ± 0.8	20	90	4–9	29	12	9	5
E. M.	8/5	25	28.7 ± 0.7	24	56	1–4	17	4	5	3
R. E.	8/11	24	29.6 ± 1.0	20	85	2–9	32	9	9	9
M. N.	8/12	24	29.6 ± 1.1	20	66	2–4	22	4	2	
Normal control:										
C. F. (current, no ABMC)	7/1	22	27.8 ± 0.0	25	62	1	2			
C. F. (current, no ABMC)	7/6	22	30.0 ± 0.3	20	44	3	3			
C. F. (current, no ABMC)	7/2	22	29.5 ± 0.5	30	86	1–3	7			
C. F.† (no cur., no ABMC)	7/14	24	27.9 ± 1.3	..	..	2	6	6	7	
C. F.† (no cur., no ABMC)	7/21	23	27.2 ± 0.7	..	..	1	1	2	1	
C. F.† (cur., no ABMC)	7/29	26	30.1 ± 0.9	20	90	1–9	4	7	5	
R. E. (cur., no ABMC)	8/19	25	28.8 ± 0.3	20	64	4–18	21	3		
Patient:										
H. H. (T. A. O. hand)	7/30	26	29.4 ± 0.4	30	46	10–14	24	18	17	
J. S. (T. A. O. hand)	8/4	25	28.5 ± 0.5	22	50	1	13	2		
B. G. T. A. O. hand)	8/7	24	28.9 ± 0.7‡	24	72	1–2	12	1	2	3
Reflex heat: (no cur., no ABMC)										
E. M.	8/2	24	28.8 ± 0.3	..	..	2	30	8§		
R. E.	8/18	24	29.0 ± 0.7	..	..	3–11	24	6§		

* Young adults, male except for "E. M."
† Simultaneous ABMC iontophoresis to opposite hand.
‡ Temperature in plethysmograph raised to 33.5° 1 hour after iontophoresis: no rise in blood flow resulted.
§ Fifteen minutes after treatment.

No conspicuous signs of systemic effects were ever observed. In several instances there was a slight increase in intestinal peristalsis and in one there was a slight fall in systolic blood pressure, but these were exceptional. Pulse rate was not significantly affected. The treated hand sometimes showed slight reddening and occasionally there was sweating of this hand for 1 or 2 hours after the treatment; but usually the prolonged exposure to the fluid in the plethys-

mograph produced thickening, corrugation, and whitening of the skin and neither hyperemia nor sweating could be detected. There was, however, a pounding sensation in the hand at the height of the ABMC effect. This was synchronous with the pulse and the pulsations of the fluid in the plethysmograph were visibly increased at this time. No burns resulted. In one case there was mild tanning of the skin area exposed to iontophoresis and this lasted several days.

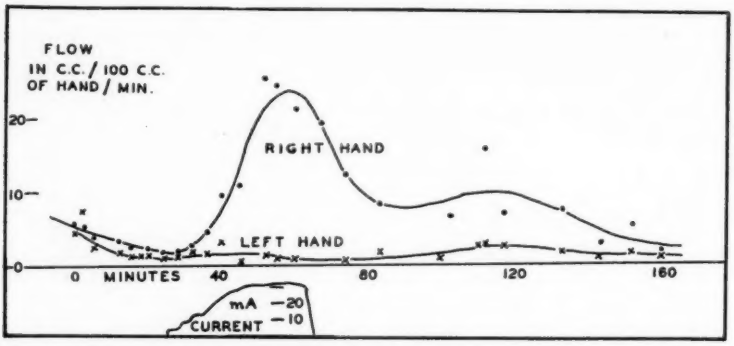

FIG. 1.—Representative blood flow in the hands of a normal subject. Right hand of C. F. (Table 1, 7/21/37) treated by ABMC iontophoresis, left not treated.

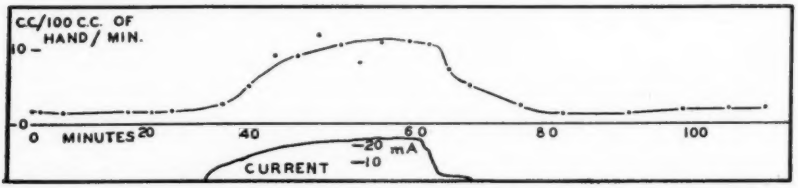

FIG. 2.—Representative curve of blood flow in the hand of a patient with obliterative disease of the arteries of this hand, hand (of B. G.) treated by ABMC iontophoresis.

These results fully confirm the belief that iontophoresis with ABMC produces marked dilation of the blood vessels in the treated part. The effect seems to be too great to be attributed to changes in the most superficial vessels alone and it is probably exerted upon deeper vessels as well. If the beneficial action depends entirely on an increased blood flow it occurs mainly in the part treated.

In 2 subjects ABMC iontophoresis was replaced by reflex vasodilatation in their hands produced by application of heat to the legs (Table 1, end). Blood flows of 30 cc. and 24 cc. per 100 cc. of hand per minute were obtained. On another day, ABMC iontophoresis produced blood flows of 17 and 32 cc. in these subjects. In 12 normal subjects Prinzmetal and Wilson[11] found that the aver-

age flow through the forearm was 3.6 cc. in response to heating the opposite arm in water at 45° C. They obtained in 17 normal subjects an average flow of 14.6 cc. during reactive hyperemia (temp. plethysmograph, 24° C.), 14.9 cc. when the arm was heated at 45° C., and 29.5 cc. during reactive hyperemia plus direct heat (temp. plethysmograph, 40° C.). The average flow in the hand in all our cases treated with ABMC iontophoresis was 23 cc. per 100 cc. per minute.

Studies in Dogs. Although the question of greatest interest was answered unequivocally by our studies in man, showing that blood flow is markedly increased in the treated part by ABMC iontophoresis with no, or with inconsiderable, systemic effects of the drug, a number of other questions of practical importance necessarily remained unanswered. Among these are the factors involved in the production of burns during iontophoresis, the

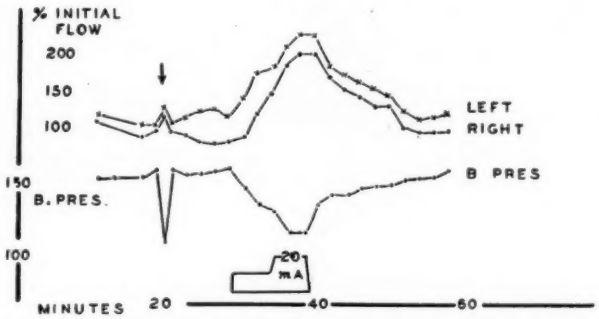

FIG. 3.—Dog 6, chloralose and ether anesthesia—blood flow in legs. ABMC electrode right leg, saline left. Same current through each leg (arrow indicates the time of injection of a minute dose of acetyl choline intravenously, with transient effect).

part played by strength of current, strength of solution, and the size of the electrodes. In the hope of securing information on these and similar points, we carried out a series of 20 experiments on dogs anesthetized with chloralose and ether. Carotid blood pressure was recorded directly by means of a mercury manometer. ABMC iontophoresis was carried out on one leg.* Arterial blood pressure was reduced distinctly within several minutes when 0.2% ABMC and 6 or more mA of current was used, and other signs of the systemic effects of the drug (profuse salivation, increased peristalsis) soon became apparent. The fall in blood pressure did not depend upon the action of the anesthetic because it, as well as increased peristalsis, and increased salivation, occurred as promptly and as intensely in an unanesthetized dog.

The observations on systemic effects on the whole confirm those obtained

* In the greater number of these dog experiments, blood flow through both femoral arteries (or veins) was measured by the thermo-electric method of Schmidt and Walker.[14] We found that under the conditions of the experiments ABMC iontophoresis produced systemic effects of the drug as promptly as it produced an increase in blood flow through the treated limb (Fig. 3). We were unable, by varying the strength of the drug, the amperage of the current, and the size and shape of the electrodes, even by using a metal-lined plethysmograph as the positive electrode, to produce in the dog the purely localized vasodilator effect that was so conspicuous in man.

by Kotkis and Melchionna[5] on dogs and by Molitor[9] in rabbits, and yielded a certain amount of information which bears on the clinical use of ABMC iontophoresis. We found that the extent of the fall in blood pressure (and therefore the degree of effectiveness of the procedure) varied directly with the strength of the solution* (Fig. 4) and the amperage of the current (Fig. 5), and that the effect was due to the drug rather than to the passage of the current alone, since it was absent when saline was substituted for the drug. In addition, we found that varying the size of the positive electrode over a wide range did not affect the degree to which the blood pressure was reduced by given strengths of current and solution (Fig. 6). This, together with the fact that with smaller electrodes in man there was more local

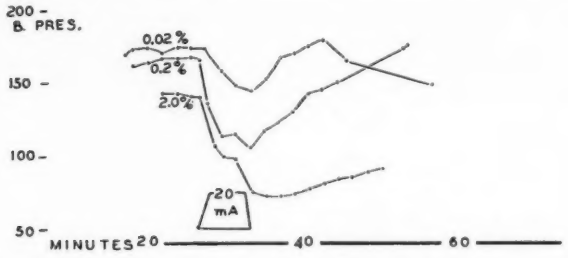

FIG. 4.—Dog 20, chloralose and ether anesthesia—effect on blood pressure of various concentrations of ABMC during iontophoresis. Curves show mean blood pressure.

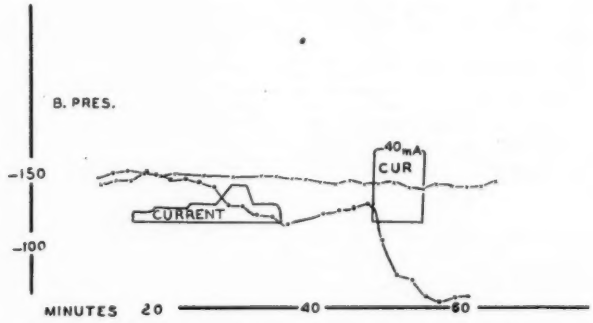

FIG. 5.—Dog 10, chloralose and ether anesthesia—effect on blood pressure of strength of current used during ABMC iontophoresis. Flat curve is control with no current. Curves show mean blood pressure. (Maximum current at left 20 mA, right 40 mA.

sweating and erythema than with larger ones, shows that a denser current (the same current through a smaller area) carries the same amount of ABMC into the body and increases the superficial local effect. Consequently, if one uses a very small electrode the amperage of the current must be reduced if a severe erythema or burn is to be avoided. On the other hand, if a very large electrode is used a current sufficient to produce the desired local effect might elicit severe general effects.

* Kotkis and Melchionna found that a 0.5% solution of Mecholyl depressed the blood pressure to the same degree that a 0.012% solution did but was more effective than a 0.010% solution. Their results do not agree quantitatively with Molitor's or ours.

Studies on electrode burns in dogs bear out the conclusion that the local effect varies directly with the density of the current. With a current of 20 milliamperes when only the thin edge of a metal electrode was in direct contact with the skin, vesiculation occurred in 1 minute if it was the negative electrode, in 5 minutes if it was the positive. When the flat surface of the metal (8 sq. cm.) was used instead, the same current caused vesiculation in 4 minutes at the negative electrode, while no burn was produced in 20 minutes when the same electrode was positive. Evidently burns are more rapidly produced at the negative electrode than at the positive, and do not occur when the current is widely dispersed.*

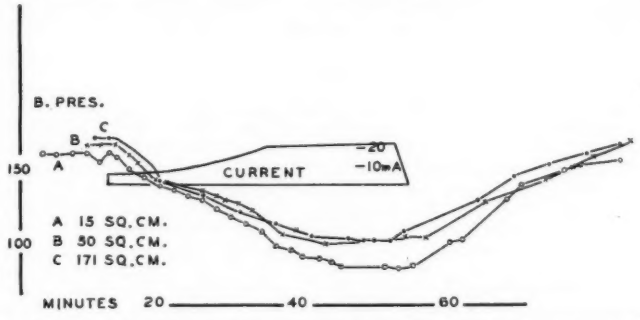

FIG. 6.—Dog 12, chloralose and ether anesthesia—effect on blood pressure of size of positive electrode during ABMC iontophoresis.

The simple rules learned to obviate burns are: 1, Do not use a small electrode unless the current is appropriately decreased; 2, never let metal touch skin; 3, do not regard the negative electrode as unimportant, but keep it as large as possible and be particularly careful to keep its metal from touching skin.

Summary. 1. Numerous measurements of blood flow in the hands before, during, and after acetyl-β-methylcholine chloride iontophoresis were made in human subjects. There was consistently a great increase in blood flow.

2. Blood flow in the affected hands of 3 patients with obliterative disease of the arteries was greatly increased by ABMC iontophoresis. There was some lasting effect in these patients as well as in normal subjects.

3. Systemic effects of the drug were rare. In the untreated hand there was no increase in blood flow. Current alone produced a slight increase in flow. ABMC without current did not alter blood flow.

4. In the two subjects studied, ABMC iontophoresis increased peripheral blood flow to about the same extent as did reflex vasodilatation. The effect by iontophoresis was more lasting. The therapeutic possibilities of reflex vasodilation have not been tested.

* Dr. Hans Molitor tells us that he has seen much the same, and has seen burns produced when a cloth-covered electrode becomes dry in all but several small spots. Burns occurred at these spots.

5. In dogs systemic rather than local effects of the drug predominated. Whether this is a species difference, or is related to the difference in experimental conditions is not known. The systemic effect varies with the concentration of the drug and the strength of the current, but is independent of the size of the electrode within the range of sizes used. In anesthetized dogs there was usually a mild, generalized increase in peripheral blood flow during ABMC iontophoresis.

We wish to thank Prof. Carl F. Schmidt for helping us to assemble and use the thermostromuhrs, Dr. Norman E. Freeman for lending us his plethysmographs, and Merck & Co. for donating the drug (Mecholyl).

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CHANGES IN BLOOD LIPIDS DURING INSULIN TREATMENT OF SCHIZOPHRENIA.

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Sakel's insulin-hypoglycemia treatment of schizophrenia, which has been carried out on a number of patients in this hospital (Cameron and Hoskins[4]), afforded an opportunity to study the acute and chronic effects of large repeated doses of insulin on various physiologic variables in the human organism. This report deals with the variations of blood lipids during the course of the insulin treatment in 16 cases, 5 of whom showed a good remission during the treatment. The acute physiologic effects of insulin on the post-absorptive level of blood lipids were studied during the course of the hypoglycemic reaction. The chronic effects of repeated doses of insulin on blood lipids were studied at intervals of 2 weeks during

the course of the treatment, and the variations occurring were correlated with the clinical status of the patient and with changes in body weight. If a good correlation between blood lipid levels and clinical status could be found, we might have a physiologic index of a patient's progress under various regimens of treatment.

Numerous attempts have been made to determine whether or not there is an abnormal lipid metabolism in schizophrenia. These attempts have consisted in the study of the absolute level of blood lipids in patients compared with that in normal controls, the comparison of early cases with long-standing cases, and the correlation of the changes in lipid level in patients with variations in their emotional content or clinical status. Stenberg,[22] from a study of previous literature, concluded that a difference in the blood lipid level of schizophrenic patients and normal controls had not been demonstrated. He criticized the previous work for the use of inadequate chemical and statistical methods and the small number of cases. Using Bang's methods, Stenberg compared the total cholesterol and total fatty acids in 62 female and 9 male patients, with 25 female and 9 male controls. He was not able to find a statistically significant difference between patients and normals, although the mean blood lipid levels were slightly higher in the patients. Brice,[2] using Bloor's methods, compared 62 schizophrenic patients with 25 normal controls. The mean values for total cholesterol and total fatty acids were slightly lower in the patients than in the normal, but the difference was not statistically significant; however, he claimed that his data presented evidence of a real depression of blood lipids. A report from this laboratory by Looney and Childs[12] indicated that schizophrenia might be characterized by a slight depression of the blood cholesterol. This conclusion was based on a study of 50 male patients and 26 normal controls, using the method of Myers and Wardell.[16] Further intensive studies have shown a seasonal variation of blood cholesterol in patients (Jellinek and Looney[9]). Unpublished data indicate that when this seasonal variation is taken into account by studying patients and normals in pairs, there is no significant difference in blood cholesterol between the two groups. Because of the great intraindividual variation of blood lipid from day to day and the even greater interindividual variation in both patients and normal controls, only a very large difference would be statistically significant. An essential aspect of this investigation is the determination of the intraindividual changes of the blood lipids during the psychosis and after recovery.

That the duration of the illness and emotional factors may play a part in determining the absolute levels of blood lipids in schizophrenic patients has been indicated. Sharpe[20] thought that blood cholesterol was decreased about 25% below normal early in schizophrenia and then increased to 30% above normal in long-standing

cases. Lipid phosphorus did not show any significant variation from the normal. In 24 cases of less than 1 year's duration, Stenberg[22] found that blood cholesterol and total fatty acids were higher than normal and these values returned to normal during remission. In 38 cases of long duration, the mean blood lipid levels did not differ from the normal. However, those patients with heightened emotions showed high blood lipids; those with dulled emotions showed low values; and those without emotional disturbances showed normal values. In contrast to this apparently direct relationship between the blood lipid levels and the emotional tone of the patients, Duncan[6] thought that there was an inverse relationship between emotional tone and blood cholesterol. High values were found in 47 of 76 patients who were in quiet or dull mental states, and low values were found in 38 patients who were in confused or excessive emotional states. During periods of excitement, lower cholesterol was found in 21 of 25 patients than during intervals of quiet or apathy. Brice,[2] corroborating Stenberg's work, found that the depression of the level of blood fats was most pronounced in the apathetic, stuporous types of cases. Emotionally excited cases had higher values. Looney and Childs[12] did not find any significant relation between blood cholesterol and the emotional status of the patients.

Experimental Methods. The technique of the insulin hypoglycemic treatment, following Sakel's method, has been described by Cameron and Hoskins.[4] The treatment consisted in giving 20 units of insulin subcutaneously to the fasting patient. In some cases this was given daily and in a few cases twice daily. The dosage was gradually increased until a hyperinsulin reaction was produced, and thereafter the dosage was dependent on the clinical progress of the patient. In the majority of cases the dosage was increased until coma was produced. The hypoglycemic reaction was terminated by the administration of sugar when the most desirable mental state of the patient was reached. The clinical progress of the patient was estimated from day to day by the psychiatrist. Each patient was observed over several hours each day, and, following the treatment, was interviewed. The patient's affective response, his capacity to mix with others, his work output, his interest in personal appearance, and his sex attitude were taken into account. The psychiatrist's observations were checked against the daily reports of the nurses and periodic reports of the Occupational Therapy department. The relatives were also interviewed and their statements considered in reaching a final judgment.

Blood lipids were studied before beginning treatment and at intervals of 2 weeks to 1 month during the course of the treatment. Blood samples were taken in the morning, in the postabsorptive state (14 hours after the last meal) before the insulin injections. Since the blood samples were taken at least 20 hours after the preceding insulin injection, the acute effects of the insulin hypoglycemic reaction on blood lipids should have subsided. To study the effects of the acute hypoglycemic reaction itself on blood lipids, a few blood samples were taken during the reaction, usually 2 to 3 hours after the insulin injection when the patient was in coma and the blood sugar at a low level. Phospholipid, total lipid, and total cholesterol were determined on whole blood by Bloor's method.[1a,b]

Results. In 14 of the 16 cases studied, a significant rise in the blood lipids occurred during the early weeks of treatment. The mean rise in these cases is shown in the accompanying chart. This initial rise is statistically significant for phospholipid, total lipid, and total cholesterol.* Of the 14 cases who showed an initial rise of blood lipids during the early weeks of treatment, 9 showed a return to the pre-medication levels as the treatment proceeded.

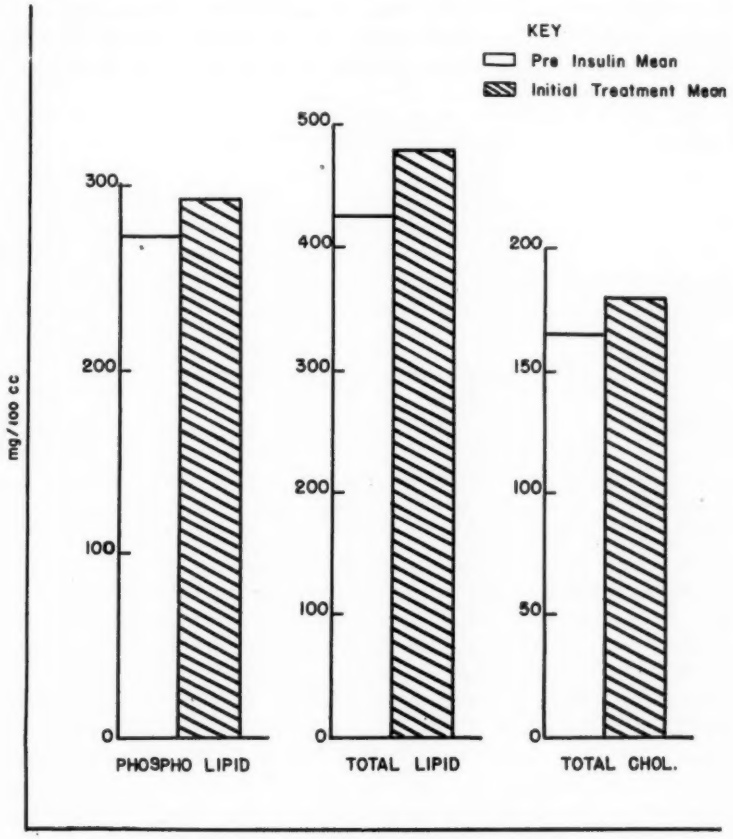

CHART 1.—Mean rise in blood lipids during initial insulin treatment.

Following the initial rise only random variations about the pre-medication level occurred. Minor variations in the clinical status of the patients were also noted, but no significant correlation between the clinical condition and the blood lipid variations could

* The significance was tested by means of Fisher's "t." The probabilities attaching to the "t's" show that such differences as observed here would occur by chance less than once in 100 trials.

be recognized. Most of the cases also showed a considerable gain in weight during the treatment, but no significant correlation between weight changes and the blood lipid variations was apparent.

Five of our cases showed a good remission during the treatment. These 5 cases all showed a significant rise in blood lipids over the pre-medication level. The accompanying table shows the means and ranges of phospholipid, total lipid, and total cholesterol in these cases during the initial state before recovery and during remission. The means were calculated from at least three determinations, at intervals of 2 weeks. The mean values for phospholipid, total lipid, and total cholesterol were significantly higher during remission than in the initial state.

TABLE 1.—MEANS AND RANGES OF BLOOD LIPIDS IN PATIENTS BEFORE AND AFTER REMISSION.

Patient.	Phospholipid, mg. per 100 cc.		Total lipid, mg. per 100 cc.		Total cholesterol, mg. per 100 cc.	
	Mean.	Range.	Mean.	Range.	Mean.	Range.
1. Initial	256	250–260	384	380–405	147	138–155
Remission	276	254–305	435	390–465	163	155–177
2. Initial	225	220–230	375	365–380	142	140–144
Remission	283	266–300	455	430–480	154	153–155
3. Initial	277	260–285	405	380–420	166	160–168
Remission	288	285–291	483	465–510	206	184–217
4. Initial	281	270–290	505	490–520	180	175–185
Remission	343	330–370	593	580–605	194	185–208
5. Initial	287	270–302	433	420–450	169	163–174
Remission	316	300–332	543	475–605	200	180–230

The effect of insulin on the postabsorptive level of the blood lipids was determined 9 times on 5 patients. The blood lipids were studied before and 2 to 3 hours after an insulin injection. Only minor and random variations from the postabsorptive level were found during the course of the hypoglycemic reaction so that no data are presented. Reports of the effects of insulin on the postabsorptive level of blood lipids are variable. In normal men, Christomanos[5] found that blood fats fell slightly after insulin, but Bruger and Mosenthal[3] did not find any consistent effect of insulin on plasma cholesterol. Rony and Ching[18] and Miller[15] could not demonstrate any significant effect of insulin on blood lipids. However, a rise was reported by White[24] and a fall by Wertheimer,[23] Schmidt and Ssaatchian,[19] and Himwich and Spiers.[7] In rabbits, Page, Pasternak, and Burt[17] reported a fall in serum lipids after insulin. It is apparent that the effects of insulin on the postabsorptive level of blood lipids are not very marked or consistent, the contradictory results reported by various workers depending on the use of different and often an inadequate number of experimental subjects, various dosages, and various technical methods.

Discussion. In the interpretation of the mild lipemia produced in the schizophrenic patient by daily hypoglycemic doses of insulin, it must be kept in mind that we are dealing with an organism char-

acterized by a hypometabolism. This is indicated by the malnourishment, low body weight, low oxygen consumption rate, and low blood pressure found in schizophrenia (Hoskins[8]). The schizophrenic patient is also characterized by his inefficient homeostatic mechanisms. Because of these abnormal factors, a patient may not be able to maintain his optimum blood lipid level.

Insulin may have, as one of its functions, the ability to control the type of foodstuffs burned, giving preference to the burning of carbohydrate. In the severely diabetic, the high blood lipids may indicate that the subject is using more fat for energy because of the inability of the organism to burn adequate amounts of carbohydrate. Treatment of the diabetic with insulin lowers the blood lipid coincident with the improvement in carbohydrate metabolism (Joslin[10]). Macleod[13] found that insulin decreases the lipemia of diabetic dogs. Wertheimer[23] showed that insulin prevents the lipemia of phlorizin poisoning and causes phlorizin lipemia to disappear. Shih-Hoa and Mills[21] found that insulin decreases blood lipids in the lipemia of nephrosis. Thus there is no reasonable doubt that insulin lowers an abnormally high blood lipid level. This effect is probably due to the decreased oxidation of fat coincident with the improvement in carbohydrate metabolism.

In contrast to the lowering effect of insulin on a high blood lipid level, we find a raised level with prolonged administration in the schizophrenic subject. It is possible that the continued administration of large amounts of insulin has sensitized the anti-insulin mechanisms of the body which are under the control of the adrenal and pituitary glands. This has been indicated by the finding of Looney and Cameron[11] of a reduced sugar tolerance in the schizophrenic subject treated with insulin. It is possible that the stimulation of the pituitary has caused an increased supply of the fat hormone and therefore a greater utilization of fat.

That the insulin treatment has some effect on the nutritional state of the subjects is indicated by the improved appetite and the increasing body weight of the subjects during the course of the treatment. The daily depletion of carbohydrate stores by the insulin reaction may be the stimulus for the increased food intake. The resulting plethora of food may operate to raise the blood fats above the pre-treatment level. Bloor[1c] has shown that the blood lipid level in animals parallels the amount of fat in the diet. Man and Gildea[14] found that inanition tends to cause a fall in both cholesterol and phospholipid in plasma and that improvement in nutrition raises these constituents to normal levels. Although the initial rise of blood lipids was coincident with the initial rise in body weight, the fact that the subsequent changes in body weight were not accompanied by corresponding changes in blood lipids signifies the operation of some other variable factors.

The maintenance of an elevated blood lipid level during and

after cessation of the insulin treatment in those cases which improve mentally under the treatment suggests that the blood lipids may serve as an index of the mental state of the patients. The rise in blood lipid may signify an improvement in the general metabolism of the patient and coincides with the improvement in mental state. This tendency of the blood lipids to rise coincident with the improvement in mental state indicates that the initial blood lipid level of the schizophrenic is below his optimum. If this is found to be true then the blood lipids should rise with improvement in mental state under other regimens of treatment or in natural remission. It must be emphasized that the blood lipid values are not outside the range of normal variation. A change of blood lipid level is significant only when the level for a given patient is compared before and after treatment and remission. One could not predict the mental status of a patient by comparing his blood lipid level with that of a normal group.

The schizophrenic process may be conceived as due to an interference with the normal oxidative reactions of the cells of the brain. The cells there become clogged with metabolites, among which the lipids may be a primary substance. The action of insulin in improving the clinical condition of the schizophrenic patient may be postulated as being brought about by an increase in the effectiveness of the oxidative mechanisms. This would result in an improvement in the metabolism of the lipids and necessitate a greater transportation of fats by the blood stream. The actual fat of the blood is undoubtedly a metabolite—a substance in process of utilization either by combustion, transformation, or storage. Phospholipid and cholesterol in the blood may function either as aids in the transport of fat or as fat metabolites. In either case it would be expected that their level would be higher when much fat is passing through the blood on the way to the tissues to be burned than where there was little. If one assumes that the postabsorptive level of blood lipids is a measure of the rate of utilization of fats, then the elevated blood lipids of the improved patients would signify an increased utilization of fat. Recent studies from this laboratory seem to indicate that the brains of schizophrenic subjects have a lower content of phospholipid than normal subjects and this might possibly furnish an explanation for the oxidative failure of lipid metabolism in the brain cells postulated above.

Summary. 1. In 5 schizophrenic patients who showed a good remission during the insulin hypoglycemic treatment, a significant rise in whole blood phospholipid, total cholesterol, and total lipid occurred.

2. In 9 of 11 patients who did not improve during the treatment, a mild lipemia occurred during the early weeks of treatment, followed by random variations about the initial pre-medication mean.

3. Insulin did not significantly affect the postabsorptive level of the blood lipids.

Grateful acknowledgment is made to Eli Lilly & Co. for liberal supplies of insulin.

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HIGH DOSAGE ATROPINE THERAPY IN CHRONIC ENCEPHALITIC PARKINSONISM.

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Our casual experience with high dosage atropine treatment of postencephalitic parkinsonism on this neurologic service was so superior to that which we had with various other treatments that we decided to study a series of cases more carefully. This led to a search of the literature on the subject, at which time we were able to find but two references in English, although one more (Hall[19b]) has since appeared.

Of these 30 patients studied, 21 were chronic encephalitics of the parkinsonian type and 9 parkinsonian cases of arteriosclerotic leutic, traumatic or doubtful etiology. One case of multiple sclerosis was included as a check. Since the study began, we have used the therapy on 17 more postencephalitic cases with equally encouraging results.

The age distribution ranged from 20 to 60; the duration of the symptoms averaged 10 years, the shortest being 3 and the longest 23.

Method. The method used was essentially that of Kleemann and Roemer with certain modifications adapted to the conditions under which we worked. We employed a 0.5% solution of atropine sulphate which was freshly prepared every second day because of its deteriorating qualities and consequent loss of efficacy. In the beginning we administered 5 drops 3 times daily and increased the dose by 1 drop each dose. Our experience with toxic signs soon taught us to begin with 1 drop 3 times a day and to increase the dose by 1 drop every second day and we have found this method to be the most satisfactory.

Once the dosage is reached at which a maximum amount of improvement has occurred, capsules or tablets containing the appropriate dosage are substituted for the drops. This is much more convenient for self-medication of ambulant cases. It also insures stability. The use of such tablets or capsules during the preliminary period of trial before optimum dose for each patient is reached is impractical, since it does not permit sufficient variation in dosage.

A few comments are in order regarding the daily distribution of the dose. An even distribution of the 3 daily doses over the 24-hour period is desirable. Due to ward routine our medication was given every 3 hours from 9 A.M. to 5 P.M. Because of this spacing the patients tended to become "de-atropinized" during the night with consequent evidence of overdosage after the morning medication. Therefore it seems advisable to maintain wherever possible an even distribution of the dose.

The incidence and nature of the toxic signs which appeared in our series of cases during the period in which they were being stabilized at their appropriate dosages is given below. Many of these signs were only transitory but they are all included.

TABLE 1.—TOXIC SYMPTOMS.

	Encephalitics.	Non-encephalitics.
Dryness	19	5
Paralysis of accomodation	18	1
Tachycardia	5	1
Weight loss	3	2
Urinary difficulty	4	2
Diarrhea	1	6
Constipation	2	1
Abdominal distention and hiccoughing	2	7
Nausea and vomiting	9	6
Dizziness and light-headedness	15	5
Hallucinations	6	2
Forgetfulness and confusion	11	2
Twitching of legs	1	0
Lethargy and weakness	11	6
Flushing of face	11	2

As will be noted, dryness of the mouth occurred in nearly all the postencephalitic cases. The only exceptions in our series were those which had not reached their maximum tolerance at the time this paper was prepared, as shown by the fact that their pupils were not dilated and responded to light. Dryness of the mouth is usually the earliest of the toxic signs. It is not an indication for withdrawal and the patient should be encouraged to disregard it. It may be greatly alleviated by giving chewing gum, sour candy balls, prunes, and so forth, to stimulate salivation.

Paralysis of accommodation occurred in all our postencephalitic cases excepting the 2 mentioned above and a few others in the non-encephalitic group who never received very high dosage. This sign usually occurs early in the treatment and follows shortly after dryness of the mouth. It is not an indication for withdrawal and the patient should be encouraged to tolerate it until stabilization of dosage has occurred when it easily may be overcome by proper lenses.

The next most frequent toxic sign among our patients was that of dizziness and light-headedness. Almost as frequent were lethargy and weakness. In general, these signs are more serious than dryness of the mouth and visual symptoms. In the majority of cases in which dizziness and light-headedness or "dopeyness," as the patients usually termed it, or weakness and lethargy developed, they were overcome by the simple expedient of maintaining the dosage at the level at which they occurred, for a few days, or by decreasing the dose by 1 or 2 drops, maintaining at this level for 2 or 3 days and then gradually increasing as usual. It is worthy of note that the toxic signs just mentioned as well as all others occurred with considerably greater frequency before we had changed out technique of administration—by increasing the dose more slowly. It is important to differentiate these transient signs which occur during the increase of dosage from the lethargy, anorexia, and loss of drive which supervene when actual overdosage has taken place. These signs of overdosage usually occur in conjunction with the marked aggravation of the original parkinsonian symptoms which previously had been relieved. In the case of overdosage, gradual reduction until the signs are relieved is indicated. Never abruptly withdraw the atropine. This is very important.

Flushing of the face was another frequent toxic sign. However, we feel that this was in great part due to the uneven distribution of the doses during the day, as it occurred most frequently either in the morning after the first dose (too rapid atropinization after a long period of withdrawal during the night), or shortly after the mid-day dose (cumulative effect of the morning and mid-day dose). In several very marked cases we arranged to have the night dose given at a much later hour, with practical disappearance of the flushing. A more even distribution of the medication would practically eliminate this sign.

Nausea and vomiting, accompanied by abdominal distention and in some cases hiccoughing was fairly common among our patients, particularly during the preliminary period of trial. It was particularly common among those patients who were not encephalitics. This condition was treated with gastric lavages, enemas, rectal tube and prostigmin, as well as intravenous fluids if necessary. In general, the treatment is that of postoperative distention. Later, having changed our plan of medication from daily increase to every

other day, we met with these signs much less frequently. Furthermore, with careful observation, if the atropine is reduced at the first sign of abdominal distress, these signs were practically eliminated.

Diarrhea and constipation were relatively rare among our cases. Constipation appeared in only 2 encephalitic cases and in both it was only transient and was overcome easily with mineral oil; diarrhea occurred in only 1 encephalitic case as a terminal sign. Otherwise it occurred in 6 of our 9 non-encephalitics when the dosage was increased above a few minims. (We were never able to overcome this sign in the non-encephalitics, except by reducing to a very low dosage and maintaining it at that level.)

A very annoying but not at all serious toxic sign which occurred quite frequently (in over one-third of the cases) was that of transient confusion and forgetfulness. Particularly annoying was the fact that 2 or 3 patients would occasionally forget that they had received their morning medication and would bother the nurses for it. However, these episodes were transitory, and only in a few instances necessitated reduction or maintenance.

Hallucinations occurred in 6 of our encephalitic patients and in 2 arteriosclerotic parkinsons. They were usually transient and occurred most frequently after the morning dose. In the main, they were overcome by slight reduction for a short period of time. A number of the patients realized the hallucinatory nature of their symptoms, but could not control them. Transitory somnambulism occurred in 1 case.

Episodes of tachycardia occurred in 6 of our patients, but were neither marked nor of long duration. They occurred most frequently after the morning dose. Subjectively only 1 patient (R. B.) complained of this to any extent.

Difficulty in starting the urinary stream occurred in 4 cases. In 3 this was an early sign and was overcome without variation in the routine of administration. In the fourth case (H. F.), it appeared as a terminal sign, complicated by the fact that this patient had a large scrotal abscess and cystitis, so that the direct connection between the atropine and the urinary difficulties was not definite.

Twitching of the legs occurred in 1 patient (G. M.). It was his only toxic sign besides dryness of mouth and paralysis of accommodation. This twitching occurred with remarkable regularity whenever the dosage was increased above 13 drops. This patient has improved greatly on this dosage, and is being maintained with great satisfaction thereon.

Loss of weight was not marked in any case except in the terminal stages of the patient mentioned below (H. F.). Check on the weights of the patients over a 2-month period showed a light general increase. In the 4 cases in which loss did occur, it was merely a matter of 2 or 3 pounds, and might be accounted for by the increase in activity on the part of the patients. It is interesting to note that

the appetites of the great majority of the patients improved remarkably under atropine therapy.

Profuse perspiration occurred in 3 patients, and may be controlled (just as flushing of the face) by more careful spacing of the daily doses and with slower increase. Our patients, although annoyed by this symptom, have accepted it because of the other improvements. It should be borne in mind that profuse perspiration may be a sign of overdosage, in conjunction with loss of drive, aggravation of parkinsonian symptoms, and so forth. But one of our patients showed skin eruptions.*

The establishment of the optimal dose for each case is a difficult problem and one which must be strictly individualized. Our experience showed no relationship to the length of time which elapsed since the onset of the parkinsonian symptoms (contrary to the experience of Roemer, who states that the further away from the acute encephalitic episode the better the response, and of Marinesco and Facon, who found that recent cases reacted better than old cases which had previous therapy). In general, the optimal dose may be established in the manner described by Roemer and Kleemann, *i. e.*, when the maximum is reached, it is maintained and then reduced slowly to a point just above that at which the parkinsonian signs appear. However, we have found that the length of time necessary to establish tolerance was very variable. Due to the difficulties mentioned above, there were occasional lapses in the treatment which probably added to our stabilization time. In general, approximately 2 to 4 months are necessary to establish the optimal dose. In some few cases (*e. g.*, G. M.), toxic signs appeared at a very low dosage and reduction of a few minims gave maximum subjective and objective improvement. In others, toxic signs did not appear until very high doses had been reached, and then considerable reduction was necessary until the optimal dose was reached. Still other cases developed toxic signs at a certain definite level, and were maintained at that level or slightly below it at what appeared to be the stabilization point. After a few weeks at this dosage, the tolerance apparently increased, and the symptoms reappeared, necessitating further increase and readjustment. In 1 or 2 cases this has been so pronounced that, even after a number of months, stabilization has not yet been attained. However, this is not usual. Most cases reach a certain maximum and may then be reduced to the optimal dose with little difficulty. It has been our experience that the optimal dose is remarkably exact. Variations of 1 or 2 drops (either increase or decrease) were immediately detected by the patients and could often be confirmed by objective

* During a spell of extremely hot weather, practically all of our atropine patients developed very high temperatures accompanied by rapid pulse and hot, dry skin. A few developed confusion and delirium. In all there was a complete lack of disagreeable subjective symptoms. The treatment was not interrupted.

signs (*e. g.*, G. M., who was stabilized on 13 drops and invariably detected any variation).

The maximum stabilization dose reached by any of our patients was drops 70 t.i.d. (an equivalent of 17.5 mg. or 0.35 gr. t.i.d.), the minimum was drops 10 or an equivalent of 2.5 mg. or 0.05 gr. One patient (A. A.) was temporarily stabilized at drops 7 t.i.d. for 2 weeks, due to the appearance of toxic signs. He showed signs of lowered tolerance after that, but signed a release from the hospital before further work was done. The average dose for all our patients was drops 32 t.i.d. an equivalent of 8 mg. or 0.13 gr.

The distribution of the dosages was as follows: from 0–5 mg. t.i.d., 9 patients; 5–10 mg. t.i.d., 5 patients; 10–20 mg. t.i.d., 7 patients.

In common with the experience of most observers, we were not able to reach the enormous dosages attained by Roemer and Kleemann. None of our patients exceeded 17.5 mg. t.i.d.* However, average distribution of dosages agrees essentially with that of the original observers, with a slight preponderance in the lowest group (from 5–10 mg. t.i.d.).

Analysis of Results. The accompanying table shows graphically the results obtained with atropine therapy over the period during which this therapy has been applied.

TABLE 2.—INFLUENCE OF MEDICATION ON SYMPTOMS.

(Total number of patients 21.)

	Salivation.		Rigidity.		Tremor.		Assoc. move.		Speech.		Pulsion.		Facies.		Oculogyric.	
Postencephalitics.																
Very marked	15	0	19	0	11	1	19	0	14	0	8	0	19	0	2	0
Marked	2	0	1	4	5	2	1	8	5	2	3	1	2	6	0	0
Moderate	5	2	1	10	3	8	1	7	2	9	2	3	0	5	1	0
Slight	1	5	0	5	2	7	0	4	0	6	11	4	0	8	0	1
Absent	0	14	0	2	0	3	0	2	0	4	7	13	0	1	18	20
Non-encephalitics.																
Very marked	2	0	7	5	4	3	7	6	6	5	0	0	5	3	0	0
Marked	0	0	1	3	3	3	1	3	1	2	0	0	3	4	0	0
Moderate	1	2	0	0	2	3	0	0	1	1	0	0	0	1	0	0
Slight	1	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0
Absent	5	6	1	1	0	0	1	0	0	0	0	0	0	0	0	0

The figures in the left-hand column under each symptom represent the number of patients and degree of severity of the symptoms before treatment; the figures on the right the same at the close of treatment.

The objection may be raised that this method of judgment is purely subjective, and therefore does not give a proper picture of the cases. However, such things as the ability to speak, the ability to dress and care for one's self. the movements of the hand and wrist

* The maximum dose of atropine required before stabilization was reached as reported in our series was 70 drops t.i.d. Since finishing the paper, one case has been carried to 110 drops t.i.d. with gradual and steady improvement and stabilization has not yet been reached.

on opening and closing the fingers, and the ability to drink fluids without spilling them appear to us to be sufficiently objective. Naturally, this could not be shown in detail in a table.

A brief analysis of the results obtained in our cases follows:

Salivation. Fifteen of the 21 patients drooled to a very marked extent before therapy was begun, and the remaining 6 showed this sign to a slighter degree. Following therapy, salivation had completely disappeared in 14 of the patients, was very mild in 5 others, and the 2 who still salivated moderately had not yet reached higher doses and were not stabilized. Salivation was not marked among the non-encephalitic cases, and showed very little change with medication.

Rigidity, Disturbances in Associated Movements, and Masked Facies. These three symptoms may be treated together, as they more or less complement each other. In the 21 patients, 19 were very rigid before treatment. One of them was markedly so, and the last showed only moderate rigidity. Following treatment only 2 of the patients were judged to be normal and to have normal associated movements; 15 others showed slighter degrees of rigidity and 4 were still markedly rigid, but none showed as much rigidity as before the treatment. The associated movements did not completely parallel rigidity, as only 11 showed fairly marked improvement, while in the remaining 8 the associated movements were poor. Masked facies showed practically the same numerical distribution before therapy, but improved to a less extent than the other two symptoms. In only 1 patient there was no change at all, 11 showed moderate or masked-like facies, and in 8 it was felt that there was good expression in the face, as judged by the ability to smile, laugh, and respond to emotional stimuli. As can readily be seen the non-encephalitics showed only very slight changes under therapy.

Speech. This symptom was one of the most dramatic of all in its improvement. Before therapy was instituted 14 of the patients had such marked speech difficulties that they were practically unintelligible; 5 could be understood with difficulty and only 2 showed moderate speech impairment. Following therapy, 4 of the patients were able to speak with no difficulties whatsoever, 6 had occasional difficulties, 9 had definite speech disturbances although they could be understood. The remaining 2 could be understood with difficulty, and were 2 of those who had been completely unable to utter a word before. Of the non-encephalitics, only 1 patient showed some slight improvement in his speech, the others were unchanged.

Pulsion. This was very marked in 8 of our patients, marked in 3, moderate in 2, slight in 1 and absent in 7. These were those patients who were bedridden. Six of our ambulant patients showed no signs of pulsion after treatment, 4 had only a very slight degree of pulsion, and the other 4 still showed moderate signs.

Oculogyric Crises. These were present in only 3 of our cases, in 2 to a very marked degree, and in the other only slightly. They disappeared in 2 cases, and remained present to a slight degree only in 1 of the more severe cases.

Severe and Constant Cramp-like Jaw Movements. These which made life a torture to 1 patient were so modified as to be almost unnoticeable.

Summary. 1. As insufficient attention has been paid to high dosage atropine therapy and the technique of administering the same in cases of chronic encephalitic parkinsonism in the English and American literature, we have reported our preliminary experience with this therapy and have given an extensive bibliography.

2. Thirty cases, of which 21 were of encephalitic origin and the remaining 9 of other etiology, served as the material for our study. Since this study was commenced, 17 more cases have been added to our experience with equally good results. The period of this study was approximately 9 months.

3. A detailed analysis of the difficulties, toxic signs, and beneficial results obtained with this method is given.

4. Our experience, in accordance with those of European investigators, shows that this method is far superior to the various other methods we had used in such cases.

5. The results obtained with non-encephalitic cases have led us to feel that this method may serve almost as a differential diagnostic point.

Case Histories. CASE 1.—W. A., aged 28, white male, had encephalitis in 1932 followed shortly by tremors of all extremities associated with rigidity, oculogyric crises, and difficulty in speaking. Physical examination on admission was essentially negative. Typical parkinsonian symptomatology. Previous to atropine therapy patient had received hyoscine (gr. 1/100), fever therapy, and so forth, with no change in status. Patient started on atropine therapy on 10/7/36. Dosage was increased steadily without toxic signs until reaching min. 71 when he developed hallucinations and was completely disorientated. Dosage slowly reduced and now stabilized on min. 53 with maximum subjective and objective improvement. Oculogyric crises and speech difficulty have entirely disappeared and other symptoms are so greatly improved that he is very comfortable and seeks his discharge.

CASE 2.—M. R., aged 38, white male, had sleeping sickness at the age of 20, followed by tremors and rigidities which gradually increased in severity, so that at the age of 27 he was forced to leave his position as salesman. Was admitted to hospital in 1933 with typical parkinsonian signs, rigidities predominating and tremors slightly marked. Speech difficulties were so marked that the patient appeared almost anarthric at times. He received hyoscine in usual doses and intravenous typhoid injections with no change in status. On 10/3/36 patient was started on atropine therapy, but was extremely uncoöperative and often refused to take medication. On 11/6/36 it was noted that patient was going downhill—his rigidities were more severe, the difficulties in speech were marked and he claimed that he could not chew his food. However, atropine was continued with little change in status until 1/25/37 (when patient was receiving min. 27). He

complained of marked dizziness and grogginess. Since the atropine had not improved any of his symptoms except salivation it was decided to discontinue the therapy, much to the relief of the patient. Two days later the patient was confined to bed, complained of marked weakness and increasing rigidity, and requested resumption of the atropine. The following day the patient was again started on min. 10 and gradually increased to min. 46. This time the patient coöperated very willingly. He improved subjectively, feeling stronger and more cheerful and lively. Objectively his speech and gait improved considerably, his facial expression lost its masklike character and the rigidities were much improved. The only toxic episode was a transient period of dizziness and nausea. Dosage was increased gradually to min. 53 when the patient complained of tiredness, and weakness in the legs. Dosage reduced to min. 50, and patient was stabilized at this dose with improvement as noted above. Patient is very active on ward and has been gaining considerable weight.

Case 3.—W. S., aged 50, white male, admitted to hospital on 1/25/30. Onset of tremor and rigidity in 1923 following sleeping sickness of 4 months' duration. Gradual progressive increase of symptoms which necessitated hospitalization. Soon after admission patient became non-ambulant, practically confined to bed, only up in wheel chair at times. Findings on admission were those of a typical parkinsonism—marked facies, greasy skin, excessive salivation, extreme difficulty in speaking, fine tremor of the right hand, normal reflexes, and so forth. Laboratory studies entirely negative. The usual therapy, hyoscine, atropine in usual doses, stramonium, fever therapy, and so forth, were tried with no success. About 6 weeks after atropine therapy (dosage of min. 20 t.i.d.) patient was able to hold his body straighter and to walk a few steps unsupported. The improvement continued for 3 months (dosage of min. 42) after which patient became weak, felt nauseous, lost his appetite, and developed marked flushing of the face. The dosage was gradually reduced over a period of several weeks to min. 39, at which dose the toxic signs disappeared. After a few days at this dosage, it was gradually increased without the appearance of toxic signs. The objective improvement was as follows: speech was clear and understandable, opening and closing of fists showed normal associated movements (patient states: "it used to take me a half hour to open one hand, now it takes me a second!"). The patient was ambulant and able to walk around the ward unassisted, feed himself, dress himself. Subjectively the patient was cheerful and coöperative, became interested in ward activities and planned to go home. By the end of May, 1937, the patient was walking around the ward freely and appeared almost completely free of his original symptoms. At this time he was receiving min. 73, t.i.d. On 6/15/37, at min. 80 t.i.d. the patient developed toxic signs as follows: weakness, inability to walk, increased tremors, a slightly cachectic appearance. Gradual reduction led to stabilization at min. 70, with maximum subjective and objective improvement. He felt fine at that dose and has been discharged for follow-up in the clinic.

Case 4.—S. K., aged 36, white male, admitted to hospital on 5/15/36. History of encephalitis with diplopia and "sleeping" for 1 month in 1921. In 1927, the patient developed difficulty in swallowing, excessive salivation, with tendency to cramplike opening of the mouth accompanied by cramplike shutting of the eyes. The findings on admission were as follows: masklike facies with the above cramplike movements of jaw and eyes, pupils unequal, slight left central facial, cogwheel phenomenon in upper extremities, bilateral Babinskis, no tremors, generalized rigidity. Laboratory studies entirely negative. The usual parkinsonian therapy gave no relief. Patient was put on high dosage atropine therapy on 10/3/36. Stabilized at min. 30 for about 7 weeks with loss of toxic signs and recovery from above mentioned symptoms.

CASE 5.—H. F., aged 56, white male, readmitted to hospital on 5/13/36. Influenza in 1925, followed 2 years later by masking of the face, and loss of associated movements in the left arm, which shortly thereafter developed a mild tremor. Since 1934 there has been progressively increasing difficulty in walking, accompanied by difficulty in speech and excessive salivation. Examination on admission showed essentially the findings as mentioned above, plus old varicose ulcers of both legs and a chronic osteomyelitis of the right ankle. Laboratory studies completely negative. Previous treatment included hyoscine and stramonium with no effect. On 10/4/36 the patient was started on high dosage atropine therapy. At dosage of min. 27 the patient showed marked improvement which increased with the increasing dosage so that his tremors had practically disappeared, salivation was completely absent, his speech was clear and distinct, he was able to walk around with ease. Subjectively the patient stated that he "felt fine, better than ever before I took sick."

CASE 6.—G. M., aged 25, white female, admitted to hospital on December 27, 1929, with a history of influenza in 1918. In 1922, the patient noticed stiffness of her muscles and slowness of movements. In 1929, she noticed tremors of both arms which gradually increased so that patient had to be hospitalized. Examination on admission revealed masked facies with greasy skin, marked propulsive gait, tremors of all extremities, excessive salivation, cogwheel phenomenon in both arms and eyes, normal reflexes. Speech was slow and monotonous and difficult to understand. Laboratory studies completely negative. The usual therapy was of no avail. The patient was practically confined to her wheel-chair because of her propulsive gait, and was unable to help herself because of her tremor. On 1/28/37 she was put on high dosage atropine therapy with gradual increase until min. 15 t.i.d. was reached. At this time the patient complained of twitchings of the legs, most marked at night and in the late afternoon. The dosage was increased to min. 20, then slowly decreased to min. 13 t.i.d., at which dose the patient no longer showed twitchings of the legs. At this dose she showed the following improvements: she was able to feed herself, able to embroider, her speech was clearer, more understandable and rapid, she was able to stand up straighter, but there was still slight propulsion in her gait. Subjectively, the patient changed from the "ward grouch" to a pleasant, coöperative, interested member. She never tired of stating that she "never felt better in her life." The patient has been stabilized at min. 13, since March, 1937, with no complaints whatsoever. Several attempts to increase her above min. 13 have resulted in twitchings of the legs, so that we have considered her stabilized at this dose.

CASE 7.—I. L., aged 22, white female, admitted to hospital on 4/23/32, unable to give any history. History obtained from family as follows: sleeping sickness in 1922 at Bellevue Hospital for 3 months. Since that time gradually progressing tremors, rigidities, speech difficulties and complete inability to walk. Various forms of therapy at different hospitals were completely unsuccessful. Examination on admission showed typical parkinsonian symptoms with marked tremors and rigidities. Laboratory studies essentially negative. The patient was completely bedridden. On 1/28/37 she was started on high dosage atropine therapy. At min. 12 t.i.d. she became nauseous and vomited, and appeared disorientated. The dosage was maintained for a few days, and then increased again when the toxic signs disappeared, only to reappear at min. 20 t.i.d. The only improvement noted was that salivation had decreased to a certain extent. The dosage has been increased gradually with no recurrence of toxic signs until at the time of writing the patient was receiving 49 min. t.i.d. with no improvement except for the salivation, and as the nurse on the ward stated "perhaps a better ability to swear at us, but nothing else."

CASE 8.—L. D., aged 62, white female, admitted to hospital on 9/28/35 on the surgical service with diagnosis of phlebitis of the left leg. Tremors of both hands were noted, with the history that it had started 2 years before admission. Otherwise the history was negative for encephalitis, influenza, and so forth. Neurologic examination following transfer showed markedly arteriosclerotic fundal vessels, irregular pupils, cogwheel phenomenon of the eyes, slightly greasy facies, tremor of the tongue, hands, and slightly of the legs. Generalized hyperreflexia and bilateral Babinski. The diagnosis of parkinsonism on an arteriosclerotic basis was made. Therapy, as usual, did not change her condition any. On 1/28/37 the patient was put on atropine therapy. She reached the dosage of min. 12 with no toxic signs, but at this dose began vomiting. There was absolutely no sign of improvement. Gradual reduction was of no avail and the patient continued to vomit as long as medication was continued and after a short while therapy was discontinued.

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APPENDIX ON THE SO-CALLED BULGARIAN CURE.*

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* There is a very extensive literature on the so-called Bulgarian cure, but in order not to burden the bibliography and because of the opinions expressed in the text, we give here only a few references.

STUDIES OF THE BLOOD PROTEINS IN DELIRIUM TREMENS.

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There is much evidence that the polyneuritic, pellagrous and cardiovascular complications which appear in the course of some cases of chronic alcoholism are due to nutritional deficiencies and not to the "toxic" effects of alcohol (Shattuck,[12] Wechsler,[15] Minot, Strauss and Cobb,[8] Jolliffe, Colbert and Joffe,[5] Spies and DeWolf,[14] Weiss and Wilkins[16]). Whether alterations in nutrition contribute to the onset of the more acute alcoholic disorder, delirium tremens, is, however, not established. It is generally assumed that a low intake of food, fear and loss of sleep contribute to the development of the delirium. Chemical studies which have been made on patients suffering from delirium tremens fail to throw much light on their nutritional state.

This paper presents the results of observations of the total serum protein, serum albumin, and serum globulin in 24 male patients whose ages varied between 25 and 49 years. All gave a history of excessive drinking which was increased in amount shortly before the onset of the delirium. Upon arrival at the hospital they exhibited confusion, disorientation, visual and sometimes auditory hallucinations. Except for 6 patients with mild respiratory infections, the subjects were free from pulmonary complications, head injury, kidney disease and gross clinical evidence of liver disorders, such as jaundice or palpable hepatic enlargement. Edema was not observed in any of the cases. Specimens of blood were obtained without stasis from an antecubital vein before the patient was allowed to have food, fluid or medication in any form, and again after the features of the acute psychosis had subsided. The interval between the first and second determinations varied from 4 to 10 days. Dietary histories were obtained from the relatives of the patients and from the patients themselves as soon as they were able to coöperate.

The total protein and albumin values were determined from the serum by a combination of the methods of Howe,[4] Wu,[18] and Koch and McMeekin.[7] As a check on the procedure used in the protein studies, determinations were made on 6 healthy male members of the medical staff whose ages were between 22 and 36 years. The

total protein values of these subjects ranged between 5.8 and 6.4 gm. % (average 6.1 gm. %). The albumin component ranged between 4 and 4.8 gm. % (average 4.36 gm. %). Globulin values ranged between 1.6 and 1.9 gm. % (average 1.76 gm. %).

Table 1 shows the values for the protein determinations on admission and at the time of discharge.

TABLE 1.—TOTAL SERUM PROTEIN, SERUM ALBUMIN, AND SERUM GLOBULIN ON ADMISSION AND AT THE TIME OF DISCHARGE IN 24 CASES OF DELIRIUM TREMENS.

	Values on admission.			Values on discharge.		
Number.	Total protein, gm. %.	Albumin, gm. %.	Globulin, gm. %.	Total protein, gm. %.	Albumin, gm. %.	Globulin, gm. %.
1	4.5	2.5	2.0	4.7	3.1	1.6
2	4.7	2.2	2.5	4.6	2.3	2.3
3	4.9	2.9	2.0	6.2	3.7	2.5
4	4.9	3.7	1.2	4.9	2.5	2.4
5	5.0	3.1	1.9	5.5	3.2	2.3
6	5.4	2.4	3.0	4.5	2.0	2.5
7	5.4	2.8	2.6	6.1	3.6	2.5
8	5.4	3.1	2.3	5.2	3.0	2.2
9	5.5	3.4	2.1	5.0	3.0	2.0
10	5.6	3.0	2.6	5.7	3.0	2.7
11	5.7	3.3	2.4	7.0	4.4	2.6
12	5.7	3.6	2.1	6.7	3.6	3.1
13	5.8	4.4	1.4	6.1	3.7	2.4
14	6.0	4.2	1.8	5.0	3.5	1.5
15	6.0	3.0	3.0	5.9	3.0	2.9
16	6.1	5.0	1.1	6.7	5.4	1.3
17	6.3	4.6	1.7	4.5	3.1	1.4
18	6.5	3.4	3.1	6.6	3.4	3.2
19	6.6	3.9	2.7	5.4	3.0	2.4
20	6.8	3.4	3.4	6.0	2.9	3.1
21	6.0	4.4	2.5	6.2	3.9	2.3
22	7.3	3.9	3.4	6.4	3.4	3.0
23	7.6	3.3	4.3	6.2	2.8	3.4
24	8.3	4.7	3.6	6.5	2.6	3.9

In 18 of the 24 patients, upon admission to the hospital, the serum albumin was below the lower limit of the normal range (4 gm. per 100 cc.), and in 22 of the 24 patients it was below this value upon discharge from the hospital in spite of the fact that all received high caloric and relatively high protein intakes during their hospital stay.

In attempting to evaluate the food intake of these patients before the onset of their delirium, we encountered a difficulty already known to those who are familiar with cases of delirium tremens. All of the patients stated that they ate "poorly" before the onset of the psychosis, but when one sought detailed information concerning the type and amount of food that they consumed, a variety of data was received. Some patients stated that they ate "nothing for several days" before the delirium. Others stated that they ate "only one meal a day." One man took "only soup when drinking heavily." Another could not eat for 7 days before his psychosis

appeared. A few patients who were sent to the hospital by the police tended to minimize the amount of their drinking for one reason or another and utilized whatever neglect of food there was to further their contention that they were light drinkers—that if they had eaten properly they would have avoided the delirium tremens. One might be inclined to ignore the explanations of this special lot of cases if it were not for the fact that all other cases of delirium tremens related a similar story with regard to their food intake. It is significant that all of our 24 cases, as well as many cases not included in the group, gave a history of an inadequate diet before the onset of the delirium.

Comment. It is possible that dietary deficiency is responsible for the reduction in the serum albumin. That malnutrition results in a hypoproteinemia in which the albumin is chiefly affected is well known. However, granting that there is dietary deficiency in delirium tremens, this may not be entirely responsible for the reduction in the albumin. It is known that the liver undergoes pathologic changes in some cases of chronic alcoholism. Since 1918, when Whipple[6] and his associates noted that albumin and globulin were more slowly restored after plasmapheresis by animals with injured livers, many investigators have contributed data showing that severe liver damage in man is accompanied by a reduction in the albumin of the plasma (Wiener and Wiener,[17] Myers and Keefer,[9] Peters and Eisenman,[10] Snell,[13] Foley,[3] and others). Opinions differ concerning the true rôle that the liver plays in the reduction of the albumin. Here it suffices to state that some observers (Wiener and Wiener[17] and others) have attributed the reduction to a deficiency of the albumin-forming properties of the liver, believing that this organ is the site of albumin production. Others (Peters and Eisenman[10] and others) contend that the reduction in albumin is the effect of the serious hepatic insufficiency upon the general nutrition, that malnutrition is the chief factor responsible for the low albumin. Concerning this unsettled question the cases of our series are of interest only insofar as that no signs of liver damage could be demonstrated by means of jaundice or enlarged and tender liver in any of the cases. None of the cases showed symptoms usually included in the clinical picture of delirium tremens longer than 4 days. All cases were discharged as recovered from the acute features of their attack of delirium tremens within a period of 10 days. Specific studies on the blood and urine which might enable one to detect evidences of a disturbance of liver function unrecognizable otherwise were not done. Increase of bilirubin in the blood and/or urobilinogen in the urine of patients suffering from delirium tremens has been reported by Pohlisch,[11] Büchler,[2] Binswanger,[1] and others.

It should be stated that some of the patients referred to in this report left the hospital as soon as the acute mental features of their

disorder subsided. Although the psychosis of every patient had disappeared at the time of discharge, data here presented indicate that the serum albumin of some cases had not returned to normal. The observation that the serum albumin value of 12 cases was lower at the time of discharge than it was on admission might be explained by a restoration of plasma volume to a higher level, since some of the patients seemed dehydrated at the time of admission.

Summary. 1. The total serum protein, serum albumin, and serum globulin of 24 patients with delirium tremens were determined on admission to the hospital and after the acute delirious phase of the psychosis had subsided.

2. The serum albumin of 18 cases was below 4 gm. % per 100 cc. of blood on admission. On discharge the serum albumin of 22 cases was below 4 gm. % per 100 cc. of blood, the albumin value of 12 of these 22 cases being lower than it was on admission.

3. There was no significant alteration in the serum globulin values either on admission or at the time of discharge.

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BOOK REVIEWS AND NOTICES

NEUROLOGY. A Most Comprehensive and Unified View of Modern Clinical Neurology. By ROY R. GRINKER, M.D., Chairman, the Department of Neuropsychiatry of the Michael Reese Hospital, Chicago; Formerly Associate Professor of Neurology and Psychiatry, The University of Chicago. Pp. 999; 406 illustrations. Second Edition. Springfield, Ill.: Charles C Thomas, 1937. Price, $8.50.

THE appearance of the second edition of Neurology by Dr. Roy Grinker affords this Reviewer another opportunity to view with amazement the scope of this work, to express his pleasure at the presentation of neurology as a field of biology but in the confines of a single volume. One wonders whether succeeding editions can possibly pursue this same ambition in one book without resorting to the use of sections of finer print or without discarding much of the material which makes this treatise comprehensive.

A mere cursory survey reveals that this edition represents more than a reprinting with correction of the usual minor errors which crop up in any large book.

As before, the opening chapters are concerned with the development and structure of the nervous system which are covered adequately. The profuse use of illustrations, diagrams and tables adds to the clarity of presentation. The next general section is concerned with the physiologic structure and then the function of the several important parts of the nervous system.

However one feels that such chapters as General Pathological Considerations, Technic of Neurological Examination, Tumors of the Peripheral Nerves and Spinal Cord and Intracranial Tumors are really out of place and should be withheld to their more logical places with other diseases and pathologic conditions. In this regard one feels that the chapter on the Anatomy and Physiology of the Blood Supply might follow that on the Coverings and Interstitial Tissues and the chapter on Developmental Defects might occupy a position among the pathologic conditions corresponding to that on Embryology. These however are minor suggestions. It is obvious that the chapters on the Vegetative Nervous System, the Cerebral Cortex and those on the inflammations and infections have been subjected to heavy revisions. One notes not only the inclusion of recently established facts but also brief analyses of both sides of important controversial matters. In many cases this is accomplished by quoting authors directly.

New material on electro-encephalography, migraine, myasthenia gravis, myotonia congenita, cortico-cerebellar relations and more recent concepts of the effects of vitamin deficiencies are notable additions to the present editions.

As before, the volume is profusely illustrated with beautiful pictures and photomicrographs. Numerous comparative tables of symptoms and signs add to the clarity of the context.

As usual the bibliography appended to each chapter is adequate and all references have been subject to revision. The index is comprehensive and is of great value since in a work of this character some repetition of material in the several sections is unavoidable.

The Reviewer again feels that this is the best single volume on General Neurology which has been produced in this country and one of the best in the English language.

E. T., JR.

LEGAL MEDICINE AND TOXICOLOGY. By THOMAS A. GONZALES, M.D., Acting Chief Medical Examiner of the City of New York; Associate Professor of Forensic Medicine, New York University College of Medicine, etc.; MORGAN VANCE, M.D., Assistant Medical Examiner of the City of New York; Assistant Professor of Forensic Medicine, New York University College of Medicine, etc.; and MILTON HELPERN, M.D., Assistant Medical Examiner of the City of New York, etc. With a Foreword by HARRISON S. MARTLAND, M.D., Chief Medical Examiner, Essex County (Newark), New Jersey, etc. Pp. 754; 244 illustrations. New York: D. Appleton-Century Co., Inc., 1937. Price, $10.00.

THE authors' aim "to prepare a book which would be sufficiently complete to use as a satisfactory source of reference but brief enough to serve the student as an introduction of medicolegal science" has been definitely fulfilled. Excellent judgment was used in allocating space; information necessary to the active participation of the physician in a given situation is presented in detail; police problems, etc., being mentioned briefly to indicate correlation. General legal implications are considered but finer points of law are wisely referred to a competent legal consultant.

The division of the book into two main sections, dealing with legal medicine and toxicology respectively, is orthodox. The first is more completely handled than usual as regards autopsy findings and is profusely illustrated with good photographs. Aids to decision regarding time and manner of accidental death are presented, indicating very clearly, however, the limitation of observations related thereto. The chapter on unexpected natural deaths is important; the technique and medicolegal angles of blood examination are given deserved space of 40 pages. Problems relating to sexual assault, illegitimacy, abortion and insanity are more briefly mentioned but are adequate. Toxicologic analysis is discussed separately in a section of 80 pages and should be particularly helpful to those who lack familiarity with the field. Full discussion of technique obviously could not be accomplished and, although the subject is well presented from the standpoint of postmortem examination, the procedures described usually would offer little assistance in the detection of chronic poisoning in the living. A list of pertinent references is appended to each chapter and the index is good. The Appendix, which contains condensed tables from the statistical report of the Chief Medical Examiner of the City of New York for 1935, lends definite authority to the statements and opinions of the authors.

It occurs to the Reviewer that, apart from the value of the book *per se*, it represents a serious indictment of the politically controlled, ever-changing and usually incompetent average coroner's office. Under the New York law the Chief Medical Examiner is "a doctor of medicine, and a skilled pathologist and microscopist," his assistants likewise, removable only by reason of proven incompetence or misdemeanor. Solely through such an organization, working undisturbed over a period of years, is it possible to accumulate data and experience necessary to the successful prosecution of crime and invaluable in the preparation of a book of this character. P. C.

MACLEOD'S PHYSIOLOGY IN MODERN MEDICINE. Edited by PHILIP BARD, Professor of Physiology, Johns Hopkins University School of Medicine, with 8 Collaborators. Pp. 1051; 355 illustrations and 103 tables. Eighth edition. St. Louis: The C. V. Mosby Company, 1938. Price, $8.50.

THIS new edition of this standard textbook of physiology is the first since Macleod's death, and although only 3 years have elapsed between editions, it was found necessary to rewrite the book almost completely. This has been done by a staff of editors, some of whom took part in the previous revision, but most appear for the first time, *e. g.*, H. C. Bazett, who writes the chapter on the circulation; C. F. Schmidt, the respiration; G. R. Cowgill, the alimentary tract; M. I. Gregersen, the kidney. The

advantage of such collaboration is that both text and references are up to date; this can be done only by specialists writing each in his own field. This advantage probably outweighs the disadvantages of unequal treatment of the sections and neglect of some subjects (the leukocytes are treated in 11 lines).

It should be emphasized that this book, as was true also of earlier editions, is a textbook of physiology and not as its title implies a treatise on physiology applied to medicine. There are, of course, sections on applied physiology, though these have been printed in small type, fatiguing to the Reviewer. Those readers who are chiefly interested in the application of physiology to their medical problems will find the several sections of unequal value. Thus the chapter on the alimentary canal will not be found very helpful, whereas in the chapter on respiration there are admirable discussions of such conditions as cyanosis and anoxia.

M. McC.

Approved Laboratory Technic. Clinical, Pathological, Bacteriological, Mycological, Parasitological, Serological, Biochemical, and Histological. By John A. Kolmer, M.D., Dr. P. H., Sc.D., LL.D., L.H.D., F.A.C.P., Professor of Medicine, Temple University; Director of the Research Institute of Cutaneous Medicine, Philadelphia, etc., and Fred Boerner, V.M.D., Assistant Professor of Bacteriology, School of Medicine and Graduate School of Medicine, University of Pennsylvania; Bacteriologist, Graduate Hospital, Philadelphia, Pa. Pp. 893; 380 illustrations and 12 colored plates. Second edition, rewritten, revised and reset. New York: D. Appleton-Century Company, Inc., 1938. Price, $8.00.

After 7 years a new edition of this book appears, with 5 new chapters and 28 collaborators. These collaborators figure in all but 9 of the 38 chapters, though the nature of their collaboration is not indicated. The many new methods developed in recent years have required much rewriting, which appears to have been done carefully and well.

E. K.

The British Encyclopædia of Medical Practice. Including Medicine, Surgery, Obstetrics, Gynæcology and Other Special Subjects. *Vol. 5. Endoscopy of Respiratory Tract to Goitre. Vol. 6. Gonorrhœa to Hydrotherapy.* Under the General Editorship of Sir Humphry Rolleston, Bt. G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. With the assistance in a Consultative Capacity of F. R. Fraser, M.D., F.R.C.P., G. Gray Turner, D.Ch., M.S., F.R.C.S., James Young, D.S.O., M.D., F.R.C.S. Ed., F.C.O.G., Sir Leonard Rogers, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F. R. S., F. M. R. Walshe, O.B.E., M.D., D.Sc., F.R.C.P. Vol. 5, Pp. 683; 139 illustrations. Vol. 6, Pp. 850; 89 text illustrations and 7 plates. London: Butterworth & Co. (Publishers), Ltd., 1937. Price, $12.00 per volume.

This fifth volume, continued on the lines described in earlier reviews, covers 46 subjects, ranging from Endoscopy to Goitre. Fœtus diseases, etc., in 53 pages approximates a veritable treatise on the subject. Other important topics are Enteric Fevers, Epilepsy, Fibrositis, Fungous Diseases and Gassing. One regrets that, as usual in the last named topic, the action on the hemopoietic system is apparently not appreciated. Six excellent plates and 139 text illustrations of varying merit are included.

The 39 articles of this sixth volume necessarily include a number of blood conditions and also 10 subdivisions of heart disease. "Gonorrhea," "The Hand," "Hernia" and "Hydrotherapy" each cover more than 20 pages. However, in general, one is sharply reminded that even an encyclopedia of this size should be used as a quick, handy reference book, and not be confused with other types of medical texts that can give more adequate treatment of the topics included.

E. K.

THE PHYSICIAN'S BUSINESS. Practical and Economic Aspects of Medicine. By GEORGE D. WOLF, M.D., Attending Otolaryngologist, Sydenham Hospital; Attending Laryngologist, Riverside Hospital, New York City. Foreword by HAROLD RYPINS, A.B., M.D., F.A.C.P. Pp. 384; 57 illustrations. Philadelphia: J. B. Lippincott Company, 1938. Price, $5.00.

THIS book attempts to cover in a single volume the many problems of an economic and practical nature which confront the physician during the establishment and maintenance of medical practice. The contents, although vaguely familiar to every physician, are here organized and readily accessible, in such a way as to be of practical value. I believe that its greatest worth will be to the beginner, in the organization and conduct of his early practice. L. H.

MANUAL OF HUMAN DISSECTION. By EDWIN M. SHEARER, PH.D., Associate Professor of Anatomy, New York University College of Medicine. Pp. 321; 79 illustrations (author's original drawings). Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $4.25.

"IF any apology be needed for the appearance of the present Manual, it may be stated, without any wish to disparage the labors of others, that the works of this kind hitherto published seem to the author open to one or the other of two objections—either as being too systematic, and therefore not adapted for the dissecting-room, or as obscuring the more important features of Anatomy by a multiplicity of minute and variable details." (From the preface of the "Dissector" of Luther Holden, 1851.)

"The following laboratory guide to the dissection of the human body is presented in the hope that it may be found useful by those who, like the author, have come to feel that, with the serious decrease in the number of hours allotted to the subject of gross anatomy in American medical schools of recent years, the admirable but lengthy guides at present available are not entirely satisfactory." (From the preface of the subject of this review.)

If we take Corner (Clio Medica—Anatomy) at face value, "Practically all the information to be gained by the old basic method of the science, dissection of the human body, was in hand about a hundred years ago. There is very little gross anatomy in current textbooks that was not in those of Charles Bell, Henle, or Sappey." Apparently no teacher of anatomy in the intervening years has ever found a completely satisfactory method for adjusting the length of the art to the shortness of student life. The limitation of the time devoted to the course in anatomy, however, seems to be making itself acutely felt. This may be because the teacher, with wider interests, feels that he must conserve his own time by better organization of the course. Although we have had the excellent short dissector of Heisler, a few remaining copies of the short 1910 edition of Cunningham, the "Note Book" of A. Melville Paterson (1914), the outline of Emmel, the "Introduction" of Terry, the very short dissector of McCotter—to name a few, the last year has brought forth the "Method of Anatomy" by J. C. Boileau Grant and the work of our present author.

Dr. Shearer has set for himself the task of attenuating the subject of gross anatomy. He urges the student to approach dissection with the serious respect that the material demands and with a reflection upon the manner in which the right to dissect has been gained. He gives advice as to the care of instruments, and of course, his version of the indispensable instruments. There follows a strictly morphologic account of the structures as exposed by regions, and directions for their morphologic exposure. The primary purpose of the author is hereby rigorously fulfilled. It seems too bad that the student is not told how to pull upon or twist a muscle or tendon in order to bring out the contribution of the living muscle to the complexity of joint

action. The mention of the functions of nerves is a slight deviation from the strictly morphologic character. Applied anatomic considerations, although extremely limited, are occasionally found. For example, the relations of inguinal hernias are discussed, but here the common use of the inferior epigastric vessels as an anatomic landmark for separating direct from indirect hernias is studiously avoided. In the preface, the author recounts and justifies certain omissions (for example, lymphatics), but no mention, neither in the preface nor in the body of the work, is made of the contents of the temporal bone. In view of the material on the orbit, on the nose, and on the larynx, this is a bit surprising. The statements about the dura are in line with the classical descriptions and do not reflect the recent studies of Popa and others. In brief, this is a topographic outline of the morphology (strictly speaking) of the human body, with directions for its exposure.

In the mechanical details of making the book, much thought has apparently been placed upon the binding, the paper, and the style of type. The spacing of the letters and the leading of the lines, together with the omission of subheadings seems unfortunate. The finished page has a monotony which renders ready reference difficult. O. B.

TEXTBOOK OF EXPERIMENTAL SURGERY. By JACOB MARKOWITZ, M.B. (TOR.), PH.D., M.S. in Experimental Surgery (Minn.), Research Associate, Department of Physiology, University of Toronto; formerly Professor of Physiology, Georgetown University School of Medicine, Washington, D. C., etc. Pp. 527; 330 illustrations. Baltimore: William Wood & Co., 1937. Price, $7.00.

THIS interesting volume is more than a textbook of experimental surgery. It has chapters on the antivivisection movement, and the care and feeding of animals in addition to chapters on anesthesia; equipment, technic, sutures and instruments; and 24 addition chapters covering nearly all of the phases of experimental surgical technic. It is dedicated to Frank C. Mann with whom the author was formerly associated and has a foreword by Donald C. Balfour of the Mayo Clinic. In a pleasing epilogue Doctor Markowitz states "It is our wish that this book may become a contribution to the pedagogy of surgery and surgical craftsmanship."

The entire work is carefully done. Some of the descriptive work will, to the surgeon, seem unnecessary but this work was written as much or more for the student as for the surgeon. In addition it will serve as a handbook in many experimental laboratories where surgical procedures are constantly or occasionally being used. The discussion of gastro-intestinal and biliary operations is so complete that this volume may well serve to augment and refresh the clinical surgeon's knowledge of the technic of these operations. Of course many of the operations must necessarily differ from similar procedures in man because of differences in anatomic arrangement, but the principles remain the same. Such chapters as "The Experimental Production of Chronic Peptic Ulcer" and much of the discussion of operations on the bowel, biliary tract and pancreas are offered as methods of experimental approach to problems which constantly concern the surgeon. The illustrations are excellent and profuse. The author has wisely chosen the best illustrations from many existing works on related subjects but he has added a goodly number of original drawings. Occasional typographical error (such as the misspelling of Reverdin in the legend under Figure 130) can easily be forgiven in so excellent a work which will be welcomed by research workers, students and clinicians interested in the experimental approach to surgical problems. I. R.

ALCOHOL: ONE MAN'S MEAT. By EDWARD A. STRECKER, A.M., M.D., Sc.D., Professor of Psychiatry, School of Medicine and Graduate School of Medicine, University of Pennsylvania, etc., and FRANCIS T. CHAMBERS, JR., Associate in Therapy, Institute of the Pennsylvania Hospital, Philadelphia. Pp. 230. New York: The Macmillan Company, 1938. Price, $2.50.

UNDER a rather ambiguous title, the social, psychic and physical aspects of the drink problem are discussed. The lay-author, who was previously an alcoholic habitué, offers the plan of treatment that proved successful for him, and which is said to have stood the test of time. Part I, The Psychology of Alcoholism, is given sane, psychoanalytic interpretation. Part II, The Treatment of Alcoholism, is considered under the theory of treatment, approach to treatment, and physiologic and nutritional factors. The course requires approximately 100 hours, of 1 hour consultations, distributed over the period of 1 year. At each sitting, the patient is encouraged in revealing his innermost thoughts, those intimate incidents in his life which bear upon the question, and his reactions toward them. Through the series of psychologic and reëducational treatments, a defense mechanism is set up in this emotionally immature, and previously defenseless subject, which gives him "a workable, non-alcoholic adjustment to reality." The treatment also includes drugs, suitable diet, exercise and diversion. Briefly, the objective is a newly reconstructed psyche. Throughout, there is shown but a minimum of emotional approach. However, religion is sometimes a powerful means of reclaiming drunkards, but so few have recourse to it. Perhaps men do not "fall from grace," but for the want of it.

N. Y.

THE IMMUNOLOGICAL REACTIONS OF THE FILTERABLE VIRUSES. By F. M. BURNET, E. V. KEOGH and DORA LUSH. (From the Walter and Eliza Hall Institute, Melbourne.) (Reprinted, with original page numbers, from The Australian Journal of Experimental Biology and Medical Science, Vol. XV, Supplement to Part 3.) Pp. 136; 27 illustrations. Adelaide, South Australia, and H. K. Lewis Company, Ltd., London, 1937. Price, 10/. (Obtainable from The Librarian, University of Adelaide.)

THE authors have adopted the view "that viruses and bacteriophages can most usefully be regarded as independent living microörganisms which are capable of multiplication only within the living cells of the host species." One finds, then, one-third of the material devoted to bacteriophages and two-thirds to viruses. Both plant and animal viruses have been discussed. Among the animal viruses, those of vaccinia, influenza, louping ill, Rift Valley fever, equine encephalomyelitis, Newcastle disease, infectious laryngotracheitis of fowls and myxomatosis of rabbits were discussed. Most of the material is based on the authors' experiments, and does not include a comprehensive review of the literature.

H. M.

ARCHIV FÜR KREISLAUFFORSCHUNG: Beihefte zur "Zeitschrift für Kreislaufforschung." Band 1, Heft 1–6 (July, 1937), 7–8 (Oktober, 1937). Editors: DR. EB. KOCH, Professor of Physiology, Kerckhoff-Herzforschungs-Institut Bad Nauheim, and DR. ED. STADLER, Professor and Attending Physician, City Hospital of Plauen. Dresden: Theodor Steinkopff, 1937. Pp. Heft 1–6, 224; illustrated; Heft 7–8, 80, illustrated.

THIS new Journal, the first number of which was published in July 1937, is to be supplementary to the Zeitschrift für Kreislaufforschung. Its purpose is to publish comprehensive monographs on subjects dealing with

the circulation and also to include critical reviews dealing with important circulatory problems.

The first issue contains 3 articles. The article by Max Holzmann covers 170 pages and deals with studies on chest leads in electrocardiography. The American work on this subject is confirmed. The second article by Professor Karl Hasebroek deals with the function of capillaries of organs in their relationship to the circulation of blood. The third article by Hans Havlicek attempts to support the thesis that the heart operates as a hydraulic ram rather than a pressure pump. C. W.

DIE IRRADIATION AUTONOMER REFLEXE. Untersuchungen zur Funktion des autonomen Nervensystems. By DR. ALFRED SCHWEITZER, Assistant in Department of Physiology, Middlesex Hospital Medical School, University of London. (The Radiation of Autonomic Reflexes. A contribution to the function of the autonomic nervous system.) Pp. 376; 38 illustrations. Basel: S. Karger, 1937. Price, Paper, Fr. 40; Bound, Fr. 44.

THIS book presents a strange and perplexing mixture of facts and speculations. The leading idea of the book is that stimulation of one portion of the autonomic (animalic) nervous system may spread over wide areas of both these systems. This radiation of autonomic reflexes is governed by certain rules. For example, the arterial blood pressure, acting over the pressoreceptors, influences not only "the vasomotor apparatus of the whole organism and the various activities of the heart, but also the function of the gastro-intestinal tract, the cranial and sacral parasympathetics, the endocrine glands, blood volume and composition, muscle tonus and somatic reflexes." A very useful compilation of the literature, bearing on the subject, aids in the task "to summarize the manifold viewpoints, collected in the various branches of science and to detect the laws of the experimental findings." The author tries to prove that "the radiation of autonomic reflexes is a normal property of the vegetative nervous system, founded in the organization and function of the nervous substance." Terms like the "tonus" of the sympathetic and parasympathetic system play a large rôle in the deductions. "It is the function of the sympathetic nervous system to guarantee the actual mechanical power, whereas the parasympathetic nervous system manages the energy reserves, rebuilds the used up stocks and maintains the potential preparedness of the organism." These and a number of similar generalized statements open interesting perspectives but do not seem justifiable on the ground of our present knowledge of facts nor helpful in further studies. The complicated diction of the book does not facilitate reading. F. L.

FEVER THERAPY. Abstracts and Discussions of Papers Presented at the First International Conference on Fever Therapy, College of Physicians and Surgeons, Columbia University, New York City, March 29, 30 and 31, 1937. Edited by nine members of the American Committee: DR. WALTER M. SIMPSON, Dayton, Ohio, Chairman; DR. WILLIAM BIERMAN, New York City, Secretary. Pp. 483. New York: Paul B. Hoeber, Inc., 1937. Price, $5.00.

BEGINNING in 1931, there has been held in this country an Annual Conference on Fever Therapy. In March, 1937, there met in New York City, the First International Conference on Fever Therapy, attended by physicians from 16 countries, and with 13 nations represented by delegates officially appointed by Ministries of Health. The present volume contains abstracts and discussions, each printed in English, French and German,

of the 56 papers which were read at the New York session. They constitute an instructive cross-section of the investigations and achievements in this interesting field. The next International Conference is scheduled for 1940 in Paris. R. K.

NEW BOOKS.

Cutaneous Cancer and Precancer. A Practical Monograph. By GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Syphilology and Director of Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University; and ANTHONY C. CIPOLLARO, M.D., Associate in Dermatology, Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University. With a Foreword by FRANCIS CARTER WOOD, M.D. Pp. 222; 231 illustrations. New York: The American Journal of Cancer, 1937. Price, $3.75.

The New International Clinics. Vol. 1, New Series (Old 48), March, 1938. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia. With 18 Collaborators. Pp. 322; illustrated. Philadelphia: J. B. Lippincott Company, 1938.

Fearfully and Wonderfully Made. The Human Organism in the Light of Modern Science. By RENÉE VON EULENBURG-WIENER. Pp. 472; 17 illustrations. New York: The Macmillan Company, 1938. Price, $3.50.

Digestive Tract Pain. Diagnosis and Treatment. Experimental Observations. By CHESTER M. JONES, M.D., Assistant Professor of Medicine, Harvard University; Physician, Massachusetts General Hospital. Pp. 152. New York: The Macmillan Company, 1938. Price, $2.50.

Proceedings of Meetings of the New York Pathological Society, held Nov. 19 and Dec. 17, 1936, Jan. 28, Feb. 25, Apr. 22, and May 27, 1937. (Abstracts.) (Reprinted from Archives of Pathology, March, April, July and November, respectively, 1937.) Pp. 35.

The Medical Clinics of North America, Vol. 22, No. 2 (Cleveland Clinic Number, March, 1938). Pp. 284; illustrated. Philadelphia: W. B. Saunders Company, 1938.

This Cleveland Clinic number maintains the high standard of this publication. Noteworthy are the 11 papers on different phases of allergy.

Heart Disease in General Practice. By PAUL D. WHITE, A.B., M.D., Assistant Professor of Medicine, Harvard University Medical School. Edited by MORRIS FISHBEIN, M.D. Pp. 338; 45 figures. New York: National Medical Book Company, Inc., 1937.

Syphilis, Gonorrhea and the Public Health. By NELS A. NELSON, B.S., M.D., F.A.P.H.A., Director, Division of Genitoinfectious Diseases, The Massachusetts Department of Public Health; and GLADYS L. CRAIN, R.N., Epidemiologist, Division of Genitoinfectious Diseases, The Massachusetts Department of Public Health. Pp. 359; illustrated. New York: The Macmillan Company, 1938. Price, $3.00.

Diseases of the Blood. By CYRUS C. STURGIS, M.D., B.S., Professor of Medicine, University of Michigan Medical School; Director, Thomas Henry Simpson Memorial Institute for Medical Research, and RAPHAEL ISAACS, A.B., A.M., M.D., Associate Professor of Medicine, University of Michigan Medical School; Assistant Director, Thomas Henry Simpson Memorial Institute for Medical Research. Edited by MORRIS FISHBEIN, M.D. Pp. 302; 2 figures. New York: National Medical Book Company, Inc., 1937.

The Truth About Childbirth. Lay Light on Maternal Morbidity and Mortality. By ANTHONY M. LUDOVICI. Pp. 294. New York: E. P. Dutton & Co., Inc., 1938. Price, $2.50.

Men Past Forty. By A. F. NIEMOELLER, A.B., M.A., B.S. With a Foreword by WINFIELD SCOTT PUGH, B.S., M.D. Pp. 154. New York: Harvest House, 1938. Price, $2.00.

This book written in popular terms attempts to explain sexual mechanisms in the male and many of their disorders. It suffers from the usual defects of this type of book but not glaringly so, and apparently has been written with proper motives.

Bile. Its Toxicity and Relation to Disease. By O. H. HORRALL, M.D., PH.D., F.A.C.S., Department of Physiology, The University of Chicago. Pp. 434. Chicago: The University of Chicago Press, 1938. Price, $4.00.

Hemorrhoids. By MARION C. PRUITT, M.D., L.R.C.P. S. (EDIN.), F.R.C.S. (EDIN.), F.A.C.S., Associate in Surgery, Emory University School of Medicine; Proctologist, Grady, Crawford W. Long Memorial, and Georgia Baptist Hospitals, etc. Pp. 170; 73 illustrations. St. Louis: The C. V. Mosby Company, 1938. Price, $4.00.

The Heart in Pregnancy. By JULIUS JENSEN, PH.D. (in MEDICINE), University of Minnesota, M.R.C.S. (ENGLAND), L.R.C.P. (LONDON), Assistant Professor of Clinical Medicine, Washington University School of Medicine; Assistant Physician to Barnes Hospital; Physician to St. Louis Maternity and St. Louis City Hospitals. Pp. 371; 5 figures and 117 tables. St. Louis: The C. V. Mosby Company, 1938. Price, $5.50.

A History of Women in Medicine. From the Earliest Times to the Beginning of the Nineteenth Century. By KATE CAMPBELL HURD-MEAD, M.D. Pp. 569; illustrated. Haddam, Conn.: The Haddam Press, 1938. Price, $6.00.

NEW EDITIONS.

Hernia. Anatomy, Etiology, Symptoms, Diagnosis, Differential Diagnosis, Prognosis, and the Operative and Injection Treatment. By LEIGH F. WATSON, M.D., Member of Attending Staff of California Lutheran Hospital and Methodist Hospital of Southern California, Los Angeles. Pp. 591; 281 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1938. Price, $7.50.

A Text-Book of Pathology. An Introduction to Medicine. By WILLIAM BOYD, M.D., LL.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S.C., Professor of Pathology and Bacteriology in the University of Toronto, Toronto; formerly Professor of Pathology in the University of Manitoba, Winnipeg. Pp. 1064; 459 illustrations and 16 colored plates. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $10.00.

A Text-book of Pathology. Edited by E. T. BELL, M.D., Professor of Pathology in the University of Minnesota, Minneapolis. Pp. 894; 412 illustrations and 2 colored plates. Third edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $9.50.

Symptoms of Visceral Disease. A Study of the Vegetative Nervous System and Its Relationship to Clinical Medicine. By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.P., Medical Director, Pottenger Sanatorium and Clinic for Diseases of the Chest, Monrovia, Calif.; Professor of Clinical Medicine, University of Southern California, etc. Pp. 442; 87 illustrations and 10 colored plates. Fifth edition. St. Louis: The C. V. Mosby Company, 1938. Price, $5.00.

PROGRESS
OF
MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY.

UNDER THE CHARGE OF
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PROFESSOR OF PSYCHIATRY IN THE UNIVERSITY OF COLORADO,
AND
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PROFESSOR OF NEUROPSYCHIATRY, LELAND STANFORD JUNIOR UNIVERSITY.

PSYCHIATRIC FACILITIES IN THE GENERAL HOSPITAL.

DURING the past decade, psychiatric diagnostic, teaching and research facilities in the general hospital have contributed to a better understanding of the personal and interpersonal factors in illness.

Although a recent historical survey[5] revealed that psychiatric facilities were available in the Bellevue Hospital, New York City, and the Philadelphia General Hospital in the 19th century, the establishment in 1902 of a psychiatric pavilion in the Albany Hospital attracted considerable attention. In 1923, a psychiatric service was introduced in the Henry Ford Hospital. Heldt's program in the latter hospital has been of value in demonstrating the practical as well as the more academic advantages of this type of service.

In the opinion of the Reviewer the most significant progress in the present development is due to a number of excellent services now in operation in a number of university teaching hospitals. Muncie,[7] Rennie,[8a,b] and Billings[1a,b] have described the objectives, scope and methods of their work.

Obviously, the plan of operation in each hospital is dependent upon the ability and interest of the psychiatric personnel, the receptivity of the hospital non-psychiatric clinical staff and local conditions of hospital policy. For purposes of simplicity the various services may be divided into three types.

1. Psychiatric service outside the major clinical divisions of the hospital. This is known as a consultation service, which remains independent and has no formal attachment to medicine, pediatrics, surgery, obstetrics and gynecology. The most efficient services of this type are those in the Massachusetts General Hospital, Boston; Payne Whitney Psychiatric Clinic, New York City; the Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital, Baltimore; and the New Haven Hospital, New Haven, Conn.

2. Psychiatric Service within the Department of Medicine, as exem-

plified by the work being done in the Columbia University group of hospitals, New York City.

3. Liaison organizations as operated in the Universities of Colorado and Michigan. The objectives of such programs are dependent upon the previously noted variables. Ideally, the following objectives should be reached.

(*a*) Educational program to nurses and hospital administrators.

(*b*) Supplementing the psychiatric education of medical students by the study of all cases which present major or minor personality disturbances with or without somatic illness.

(*c*) Education of the intern staff. Previous study (4[a]) revealed the need for psychiatric education in the general internship as part of the basic preparation for the practice of medicine.

4. Establishment of a rapprochement between psychiatry and the major clinical divisions of the hospital to further appreciation of the concept of personality in somatic illness.

5. Initiation of interdepartmental research in the field of psychosomatic relations.

6. Educational propaganda to the patient-public in the need to rid the latter of the omnipresent stigma of mental disease.

It is hoped that endeavors of this type will throw further light on a number of baffling clinical syndromes. The recent reviews of Dunbar[3] and Wittkower[12] have aided in drawing attention to some of the difficulties encountered in the study of psychosomatic relations.

Attention has been drawn to the more frequent personality disorders as they are encountered by the general practitioner.[4b] More specifically, the psychogenic aspects of thyrotoxicosis,[1c,6b,c] disorders of the gastro-intestinal tract,[6c,9a,b,10] and hypertension[6a] have been studied in various details.

In the field of pediatrics, Crothers[2] has considered a modification of present day pediatric services in order to adopt the more pertinent psychiatric principles necessary in understanding behavior problems in children who are somatically ill. Other suggestions have been offered in respect to surgery, obstetrics and gynecology.[4c,11]

It is hoped that the introduction of psychiatry into the general hospital will serve as a means of teaching nurses, students, interns and physicians the need for a more integrated approach to the sick person, as well as offering a fertile ground for further study of the psychogenic aspects of various clinical syndromes.

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OTO-RHINO-LARYNGOLOGY.

UNDER THE CHARGE OF

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RECENT PROGRESS IN OTONEUROLOGY.

Anatomy of the Central Vestibular Pathways. THE anatomy of the internal ear and eighth nerve has been known for many years. The pathways and connections of the auditory and vestibular nerves within the brain, on the other hand, have been the subject of much investigation and speculation since Bárány's epoch-making discoveries of the caloric and other clinical methods of testing the labyrinth.

Lorente de No,[16] on the basis of his experimental and anatomic studies, discusses the question as to whether the semicircular canals are represented by separate pathways in the brain stem as previously postulated by Jones and Fisher from their clinical observations. He states that all the fibers from the semicircular canals are parallel and the fact that they constitute two groups does not mean that each group corresponds to a canal as there are thin and medium fibers from all the canals in Group I and thick and medium fibers from all the canals in Group II. Each canal as well as the saccule is represented in every part of the vestibular nuclei and it is his opinion that the entire static labyrinth must be considered as a unit both anatomically and functionally.

Leidler,[32] in reviewing the relations between the vestibular apparatus and the vegetative nervous system, believes there are connections between the descending tracts originating from the nucleus vestibularis and the nucleus intermediolateralis and nucleus intermediomedialis which form the autonomic cell groups of the spinal cord; there are also connections with the autonomic regions of the medulla oblongata, the mesencephalon and the diencephalon. Through these connections vestibular influences are exerted upon the pupil, vascular system, heart, respiration, digestion and metabolism.

Muskens[39] sums up his work on the further connections of the vestibular nuclei which he calls the "supravestibular system." By this he means the posterior longitudinal bundle, the commissural nuclei (nucleus of the posterior commissure and the nucleus interstitialis) and the fibers running from these nuclei to the oral part of the opposite pallidum. The posterior longitudinal bundle is a highway containing both ascending fibers from the medial vestibular nuclei running to the posterior commissure and descending tracts from the pallidum by way of the commissure; these exert an influence upon forced movements in the

lateral plane of the head and eyes both in man and in animals. Similar movements in the frontal plane are governed by other tracts in the posterior longitudinal bundle which have their first point of origin in the anterior vertical canal, while movements in the sagittal plane in animals are due to interruption of pathways which run from Deiter's nucleus through the cerebellum and by way of the superior peduncle to the pallidum. His work received a certain amount of support from the clinical studies of Shapiro[47a] on patients with oculogyric crises. Six of these were studied carefully from the vestibular standpoint both during their crises and in the intervals. After reviewing the literature and postmortem material available the latter came to the conclusion that these spasms can only be explained on the basis of Muskens' theories. He expressed the opinion that the pathways as outlined by Muskens are for the purpose of bringing tonic influences from the labyrinth to the pallidum and influencing movements of the head and eyes in various planes.

Aronson[1] continued the studies of Spiegel on the cortical terminations of the labyrinth. The latter had previously shown that after applying strychnine to various parts of the cerebral cortex convulsions resulted only after a rotation stimulus following strychnine application to the posterior ectosylvian and suprasylvian gyri. Even ablation of one labyrinth produced convulsions from drugging either side, so that the labyrinth was considered to have a bilateral representation. Aronson showed that after section of the posterior longitudinal bundle this phenomenon still took place, indicating that vestibular impulses can arrive at the cortex through other pathways.

Van Gehuchten[52] sums up his views of the anatomy of the central vestibular pathways. The primary arc of the vestibular system is formed by the vestibular nerve, the vestibular nuclei and their connection with other parts of the brain. The functions of the vestibular apparatus are the reflex assurance of the bodily equilibrium and the reflex control of the eye mechanisms. This is made possible through the connections with the spinal cord (fasciculus Deiterospinalis and descending fibers of the fasciculus longitudinalis posterior) as well as the connections with eye muscle nuclei (homolaterally through the fasciculus vestibulo-mesencephalicus, hetero-laterally through the ascending fibers of the fasciculus longitudinalis posterior). The vestibular apparatus is connected through the vestibulo-cerebellar fibers with the nucleus tecti; some fibers also run to the cerebellar cortex. The nucleus tecti is a vestibular coördinating center which unites vestibular impulses with those coming from the proprioceptive tracts. Connections exist between the vestibular system and the corpora striata probably by way of the ascending fibers of the fasciculus longitudinalis posterior, nucleus ruber and thalamus as well as from the globus pallidus and the commissural nuclei. Finally afferent and efferent connections with the cortex must exist.

Anatomy of the Central Cochlear Pathways. The central pathways leading from the cochlea have not been the subject of investigation to the extent of the vestibular pathways. Some workers, however, are recording progress in this field which offers enormous difficulties. Wiley[54] endeavored to determine which parts of the cerebral cortex are used to form and retain auditory stimuli. For this purpose he

trained rats to respond to auditory stimuli and then subjected them to various small destructive lesions in the cortex. They were then retrained to their former level learning; later they were killed and their brains carefully studied. Wiley's results showed that the auditory mechanism is projected upon an area corresponding to *Fortuyn's area* which includes the postero-lateral part of the cerebral cortex. Destruction of this area may abolish an auditory habit which, however, can be reacquired. Brogden, Culler and their co-workers[8] studied the localization of sound in the auditory tracts of the guinea pig, as far as the medial geniculate bodies. They found that for purposes of hearing destruction of a single geniculate body equals the effect of destroying the cochlea or one-half of the cortex. They believe from their experiments that the frequencies follow a topographic formation from the cochlea which persists at least as far as the medial geniculate body. A number of interesting clinical observations in this field will be dealt with later in this review.

Physiology. The great stimulus given to the study of the function of the labyrinth by the discovery of the caloric reaction by Bárány, in 1906, was responsible during the following decades for a notable advance in this field. The researches of Magnus and de Kleijn and others of the Utrecht school, as well as of Fischer and Wodak of Prague had clarified the complex activities of the labyrinth and established its essential character as an organ of reflex action. Several problems that still remained to be solved, however, will be touched upon here:

The Function of the Saccule. Students of the labyrinth had very early felt that the activities of the semicircular canals differed from those of the utricle and saccule, which had receptors of a somewhat different type (maculæ) as well as otoliths in many species of animals. The former lent themselves much more readily to experimentation while isolated lesions of the latter proved difficult to produce until relatively recently. Nevertheless, the conviction persisted that the otolith organs evoked reflexes to changes in position as distinguished from the reactions to movement which could be readily demonstrated to belong to the semicircular canals. Subsequent experiments, however, indicated that of the two otolithic structures the utricle is by far the most important as far as the labyrinthine tonic-static reflexes are concerned. This is emphasized by de Kleijn and Versteegh.[27a] Continuing their experiments on guinea pigs they found that tonic labyrinthine reflexes, as well as the reaction to rectilinear movements can still be obtained after destruction of the macula of the saccule. They believe that the first group of reflexes originate from the utricle and the second from the semicircular canals. Werner[53] believes as a result of his studies on the effect of changes in air pressure on the labyrinth of guinea pigs that the saccule serves to indicate the degree of atmospheric pressure. He found, following his experiments, changes in the cellular picture of the macula sacculi but not in that of utricular macula (to increases or decreases of atmospheric pressure). In a subsequent article he reviewed his work as well as that of others on the macula utriculi and came to the conclusion that this organ is the seat of the reflexes in response to change of position. He believes that the macula utriculi is differentiated anatomically to account for the multidirectional sensitivity to static changes. Ashcroft and Hallpike[3] isolated

the saccular branch of the vestibular (in frogs) nerve and studied the action currents obtained in response to rotation or tilting of the animal as well as to vibrational stimuli; the former stimuli gave no response while the latter produced marked reactions. They believe that in man, as suggested by Tait, the saccule is concerned in the reception of bone-conducted sound.

The Origin of the Tonic-static Labyrinthine Reflexes. The rôle of the utricle in producing reactions to changes of position is doubtless of great importance. The belief, however, that the function of the semicircular canals is confined to "reactions of the head and eyes which occur during and after rotation, and reactions due to rectilinear accelerations" as summarized by Camis[10] as late as 1930, is no longer tenable in view of the work of McNally and Tait.[35] By a series of brilliant experiments in which separate canals as well as the utricle and saccule were ablated by severing the nerve outside the particular structure, these workers carried out a study of the functions of these organs in the frog. Their technique had the obvious advantage over other methods in that the effect could be confined with certainty to the desired canal or otolith organ. Their results indicated that the vertical canals as well as the utricle exerted a tonic effect upon the body musculature, especially that of the head. Loss of the anterior vertical canals resulted in marked loss of tonus on the part of the muscles involved in keeping the head up; loss of the posterior vertical canal resulted in an extended position of the head. They feel that each of the four vertical canals in the frog is a sentinel at its own portion of the head and that the vertical canals acting together with the utricles in control of the musculature of the head, body and limbs preserve the normal erect posture of the head during movement or while at rest. They found no evidence that the saccule partakes in equilibration. Hasegawa[25] repeated the centrifuging experiments by which Magnus and de Kleijn removed the otolithic membranes of guinea pigs and found that the tonic reflexes both in these animals and in frogs were still present after the otoliths were thrown off, thus lending further weight to McNally's experiments.

Reflexes to Rectilinear Accelerations. Hasegawa[25] also found that these reflexes were absent following the experiments just noted. This is in contradistinction to the conclusions of Camis that these reactions are due to stimulation of the semicircular canals and would indicate that the matter of assigning the exact origin of these reflexes is still open to discussion. The question is also discussed by Schubert.[45] His experiments indicated that in man at least rectilinear acceleration does not produce deviation of the endolymph and cupula within the semicircular canals.

Response of Statokinetic Apparatus to Sound. In the past, considerable controversy existed as to whether the semicircular canals have an auditory function. Although the nature of these structures has long been definitely established as peripheral organs of a proprioceptive nature, certain animal experiments, notably by Tullio and others, apparently tended to indicate that sound can be a stimulus for the semicircular canals. E. Huizinga[26] considered these experiments and repeated them with pigeons that had artificial openings made into their labyrinth after the cochlea had been destroyed, and obtained character-

istic head movements which corresponded to different cristæ when certain sounds were produced. Unlike Tullio, Huizinga found that these responses disappeared when the openings into the canal were closed. Guttich[24] believes in Tullio's theory as to the rôle of the combined cochlear and static apparatus in orientation. He states that even in lower animals such as crayfish reaction occurs to sound stimuli. He considers that the cochlear, neck and vestibular reflexes coöperate in serving to determine the direction of sound, which is a matter of great importance for the animal.

The Mechanism for Stimulating the Semicircular Canals. The hydrodynamic theory, which is largely held among students of vestibular physiology, considers that the stimulus which produces the reflexes arising from the semicircular canals is transmitted to the cristæ as a result of an endolymph movement or tendency toward movement which in its turn moves the cupula or jelly-like mass in which the hair cells are embedded. The bending of the cupula causes a pull upon these hair cells, thus producing the appropriate stimulus. This theory, which has been applied to explain both the phenomena resulting from rotation and from the caloric test, has been the subject of much discussion to the extent that even the existence of the cupula has been denied as an artefact. Will,[55] using special methods of staining and fixation on preparations fresh from the living animal, studied the cupula. He was able to demonstrate that it has a definite and unchangeable form, that it reaches from the crista to the roof of the ampulla and that it does not lose contact with ampullar walls and roof. He was able to make pictures of artificial cupular deviations, using the methods of Steinhausen as described for the observation in the living animal. The experiments of the latter observer are of the highest importance. Using the semicircular canals of the pike and other animals, Steinhausen[48] injected India ink and observed the cupula through the ampullar wall. He demonstrated by means of a motion picture film that ordinary movements of the head, which resulted in a shift in change of the cupula produced compensatory ocular movements and that a flow of endolymph from such stimuli as the caloric test is only effective insofar as the pressure of the fluid causes a shift of the cupula. G. Dohlman,[17] using Steinhausen's technique with some modification, arrived at similar conclusions. He states that while the endolymph current acts only for a brief moment on the cupula in such tests as the rotation test, this structure takes about 20 seconds to recover its normal position and that during this time nystagmus persists; in the caloric test there is a constant pressure and a constant nystagmus.

The Relationship of the Labyrinth to the Vegetative and Vasomotor System. LeHeux and de Kleijn[31] studied the effect of unilateral extirpation of the labyrinth on the movements of the alimentary tract in cats, using roentgenograms. In one series, bilateral vagotomy was performed and in another the sympathetic fibers to the alimentary canal were severed. They concluded that the labyrinth exerts a definite influence upon the stomach and intestines and that this influence reaches these organs through the vagus. Cantele and Pais[12] studied the effect of passive congestion on the vestibular reflexes of guinea pigs. This was induced by hanging the animal's head down for varying lengths of time. They found that the reflexes first became diminished

and finally disappeared, the last phenomena requiring 20 to 30 hours of suspension. When the normal position was resumed the vestibular reflexes returned even after experiments lasting several months. Microscopic examination of the labyrinth showed hemorrhages and edema to be much more marked in the cochlea than in the vestibular portion of the internal ear. In a previous article, Cantele[11] reviews the relationship between the labyrinth and the respiratory system on the basis of his own and others' researches. He states that caloric and mechanical irritation of the vestibular apparatus produces a reflex action characterized by negative blood pressure in the carotid and femoral arteries and that this reflex activity is probably carried by way of the tympanic plexus and the nervus intermedius. Destruction of the labyrinth is followed by some irregular oscillations in the respiratory curve. Muck[38] states that nystagmus due to vasomotor causes may occur spontaneously or may be produced by mechanical, thermal, or electric stimulation of the vertebral or radial arteries. An applicator which has been dampened with epinephrine will produce a white streak when passed along the inferior turbinate of such persons. He states that nystagmus not of labyrinthine origin can be made to disappear by stimulating the vertebral arteries, this supposedly being due to a disturbance of the blood supply in the region of Deiter's nucleus. The studies of Frazer[21] indicate that the vasoconstrictor impulses to the ear travel in the cervicosympathetic trunk and that no vasoconstrictor fibers reach the ear *via* the periarterial plexuses of the carotid or vertebral artery. This, from a theoretical standpoint would indicate a possible section of the cervicosympathetic trunk in certain cases of vertigo and tinnitus of vasomotor origin. From a practical standpoint, however, it is very difficult to differentiate between vestibular disturbances of local and central origin. Kotyza[29] demonstrates that stimulation of the vestibular apparatus exerts a considerable influence upon the vegetative system. The rotation test has a more pronounced effect upon the parasympathetic system, while the minimal caloric test decreases the tonus of the orthosympathetic system. Stimulation of the labyrinth by means of location is more marked than by the caloric test. Sudden stimulation of the vestibular apparatus increases the tonus of the vegetative nervous system and especially that of the parasympathetic system.

The Mechanism of Utricular Stimulation. The question as to whether the stimulus for the otolithic organs is constituted by the pull of the otolith upon the hair cells of the macula when the head is displaced from its accustomed position or by the pressure of the otolith is still a subject for discussion. Ulrich[51] carried out experiments on the exposed utricular otolith in a live pike. With a micromanipulator, which held a human hair, he moved the otolith about in various directions. He found that the only effective movements of the otolith in obtaining a reaction were either outwards or outwards and forwards. When the eye on the side of the stimulated utricle moved up the other one moved down. No downward movement of the homolateral eye could be produced by any movement of the otolith. Rotation about the longitudinal axis of the body to the left stimulated only the left labyrinth and rotation to the right only the right labyrinth.

The compensatory eye movements in response to change of position were tested by Gollas[23] in patients with one labyrinth destroyed. They were strapped on Grahe's table to eliminate neck reflexes and the fundus of the eye inspected with a special ophthalmoscope. The deviation of the papilla was noted in response to slow turning at 20, 40, 60 and 90 degrees from the midline and back again. Turning to the side on which the labyrinth had been destroyed gave a normal compensatory eye rotation; turning to the opposite side gave reduced ocular rotation. The author concluded that these eye movements in man are regulated chiefly by the contralateral labyrinth but also slightly by the homolateral one and that each labyrinth acts on both eyes.

Clinical Otoneurology. The past few years have been marked by an attempt to adapt tests of vestibular function in man in terms of everyday function, and in line with our knowledge of physiology of the labyrinth. There has been a noticeable trend away from the technique of the tests as elaborated by Bárány and taught by Jones and Fisher in this country, although these are still performed by many otologists here.

Compensatory Movements Tending to Preserve Equilibrium follow a characteristic pattern in animals with intact labyrinths. de Kleijn and Versteegh[27b] found that after bilateral labyrinth extirpation in animals these reactions are absent following a quick tilt about the longitudinal axis. These reactions also do not occur in man if the usual vestibular reactions are absent. After loss of one labyrinth the tilt reaction is absent at first, later returns on one side and finally on both sides. From their animal experiments they believe that this reflex probably originates from the semicircular canals.

Rademaker,[43] who has made notable contributions towards the analysis of labyrinthine reflexes in animals, has for years attempted to apply his findings to the study of the vestibular apparatus in man. In a recent monograph he sums up his work in this direction. After reviewing and illustrating with serial photographs the reactions of animals to different types of falling, rotation and tilting either around a longitudinal or a bitemporal axis, he considers the reactions of the extremities to slow and rapid tilting in man when the patient is placed on his hands and knees (eyes closed) on a specially constructed bed. By means of photographs these are shown to bear a striking similarity to the reactions of animals. He studied about 80 patients with different intracranial and labyrinthine lesions and demonstrated conclusively that these reactions, which he terms the test of static adaption, are absent only in those instances where the peripheral or central vestibular apparatus is involved. This is invariably the case only with bilateral lesions; unilateral involvement does not give a uniform picture. Labyrinthine righting reactions and tonic reflexes on the eyes in response to a change in position (not movement) are considered to be of otolithic origin; they are present in man as well as in animals but are difficult to demonstrate except in infants and individuals with certain brain conditions, owing to the influence of the visual apparatus and the higher centers.

McNally[34] sums up his ideas on the application of tilting reaction to the study of the vestibular apparatus in man. These are based upon his extensive experiments previously mentioned as well as his clinical

experience. He distinguishes between the "rapid tilt test" and the "slow tilt test." The first is primarily a test of vertical semicircular canal action but also to a lesser extent of "second mode" utricular action. The reactions take place in opposite directions. The canal action results in a compensatory reaction of the body musculature tending to send the body away from the tilt; the "second mode" utricular action tends to throw the body in the direction of the tilt. These reactions tend to some extent therefore to neutralize each other. The investigator should try to note whether there is a tendency to be thrown in the direction of the tilt (lesion of the vertical canals with intact utricle) or for overcompensation (lesion of utricle with intact vertical canals). Absence of the protective reaction would be due to loss of one or both labyrinths. The slow tilt as practised by Grahe is a test for "first mode" utricular action.

The Problem of Positional Nystagmus is one which has greatly interested clinical observers. It must be remembered that while compensatory eye movements in response to changed positions are known to be tonic reflexes of otolithic origin, no one has as yet succeeded experimentally in demonstrating that nystagmus can be produced by stimulation of the utricle or saccule. In spite of this fact, a strong belief has persisted among neurotologists that certain forms at least of positional nystagmus originate from the utriculo-saccular apparatus. Ruttin[44] reviews his experiences with the subject. He considers positional nystagmus and positional vertigo as of otolithic origin. Characteristic of pure positional nystagmus is a movement like the turning of a wheel; rotatory nystagmus is characteristic and can be called forth by bending. Vertical positional nystagmus he believes to be from the canals. The stimulus can come from either the diseased or the healthy side. He does not believe that neck reflexes can cause nystagmus. Seiferth[46] follows Ruttin's earlier classification of positional nystagmus into the type which follows a certain rule as to position required, direction of nystagmus, as well as intensity; the variety which follows no rule; and the nystagmus which shows the wheel-like turning noted above. The first and third varieties are of otolithic origin. Nystagmus is sought for with the aid of a magnifying glass in different positions. Positional nystagmus is to be differentiated from ordinary spontaneous nystagmus which is activated by change of position. The rotatory form of positional nystagmus is characteristic of peripheral disease. Positional nystagmus which follows no rule and changes its direction is typical for central involvement; that which follows a certain rule, for retrolabyrinthine and peripheral disease at its beginning. Exceptions to these general principles are not infrequent. In general, positional nystagmus is probably the first manifestation of a spontaneous nystagmus.

The Rotation Test. It has been recognized for a number of years, particularly abroad, that the technique of the rotation test as generally practised is open to very serious objections. The usual procedure of revolving the patient 10 times in approximately 20 seconds, besides constituting a maximal stimulus unlike anything which occurs under physiologic conditions, introduces a number of variable factors which decrease the value of the test. The initial acceleration, the speed of turning, and particularly the final retardation or stopping of the chair

must vary widely with different examiners and different occasions. The beginning of the turning induces a per-rotatory nystagmus in the direction of the turning which is still present when the chair is checked and post-rotatory nystagmus on the opposite direction occurs, so that the result seen by the observer must be interpreted in terms of the algebraic sum of the two stimuli. To obtain a pure post-rotatory nystagmus the Buys-Fischer method uses an electrically driven chair starting with a subthreshold acceleration and gradually gathering speed so that it takes about 3 minutes to reach a speed of 180 degrees per second; when this speed has been attained the chair is brought to a standstill by means of a special brake producing an acceleration of 680 degrees per second per second. Woletz[56] studied the post-rotatory nystagmus in 14 normal persons by means of this method He found an average duration of 28 seconds and an average of 48 nystagmic beats. After a pause averaging 15 seconds, a second post-rotatory nystagmus occurred. This lasted an average of 60 seconds for an average of 37 beats. In some cases, a third post-rotatory nystagmus with sometimes a change in direction was noted. There was a difference quantitatively between turning to the right and turning to the left in all three varieties of post-rotatory nystagmus; this was considered by the author to be due to asymmetry of the nervous system. Mittermaier[37] discusses the rotation test. His experience with the electrically driven chair showed two drawbacks; the evenness of the acceleration was secured only to a relatively small degree so that the stimulus to the semicircular canals was not an even one; and the existing means for measuring the acceleration were insufficient. The threshold value for subjective vertigo was subject to considerable individual variation and occurred prior to nystagmus. The duration of the post-rotatory nystagmus even under uniform conditions varies in different individuals and tends to decrease with repeated tests in the same individual. The author believes that a speed of 60 degrees per second or even less would be preferable to the maximum of 180 degrees per second which is attained. He believes that working with different speeds and different check methods for the chair may serve to establish some relationship between the frequency as indicated by the number of beats and the duration of the nystagmus, and thus make possible the development of a scientific minimal method of rotatory stimulation. Tumarkin[49] experimented with a method of placing the subject with his eyes closed and his ears filled with plasticine, in a tank filled with warm water, the tank being driven by a viscosity motor to eliminate all jerking; in this way all visual, auditory and kinesthetic impressions were removed. A Dodge nystagmograph apparatus was used over the closed eyelids to record the per-rotatory nystagmus which Tumarkin feels should be noted in preference to the post-rotatory variety. He found that a sense of rotation was experienced with acceleration as 0.2 degree per second per second. However, he felt that the method was still open to objections because the blinking of the patient's eyes could not be controlled as well because of the impracticability of the technique. Some idea of the smallness of the stimulus which is sufficient to produce a labyrinthine reaction can be gained from the experiments of ter Braak.[7] He found, using a small mirror fastened to the cornea of rabbits so that the deviations of the incident beam could be used to measure the ocular movements,

that an angular acceleration of less than 0.25 degree per second per second (in an exceptional 0.09 degree per second per second) was sufficient to elicit a reaction. As to stimulation by rectilinear acceleration he considers that a difference in specific gravity between the cupula and the endolymph is essential towards stimulation. If this difference is greater than 1 part in 10,000 a rectilinear acceleration of 981 cm. per second (by gravity) would be sufficient to produce a reaction. Arslan[2] carried out experiments on the effect of repeated rotation on the duration of post-rotatory nystagmus. Using a chair with a rigid control of speed and a mechanical brake he found that the effect of repeated rotations is to cause a diminution of post-rotatory nystagmus as well as a lengthening of the latent period. He considered this fact to be due to interference phenomena in the vestibular centers. That central factors are important in post-rotatory nystagmus is further attested to by Mowrer.[40] Using pigeons, he found that if rotation experiments are preceded by a rest period during which the birds are hooded and immobilized, the duration of the nystagmus is markedly reduced. This seems to corroborate the observation of the effect of excitement on the character of the vestibular response in clinical practice. In another communication, Mowrer[40] reported the effect of repeated rotation with reduction in the duration of the nystagmus. Using hooded pigeons he found that this reduction did not affect the perching ability. This result corroborates through the laboratory the well-known observation that diminished nystagmus responses such as occur in acrobats or dancers is not synonymous with any lesion but may be an acquired condition. This type of experimentation, which opens a very interesting chapter, was begun several years ago by Griffith at the time when there was an attempt to set up arbitrary standards of "normal" responses with respect to nystagmus and other vestibular induced manifestations.

Caloric Test. This method of testing was radically changed when Kobrak demonstrated that very small quantities of water only a few degrees below body temperature could produce a vestibular reaction. The idea was so startling after the mass douches taught by Bárány that for a time this fact was used as an argument against the hydrodynamic theory of semicircular canal stimulation. How little the response is in accord with the type of caloric stimulus used is brought out by Fleischmann,[20] who performed a series of irrigations on the same subject to ascertain whether changes in temperature, the amount of fluid, and the length of time during which the ear is syringed influenced the extent of the reaction. He found that in the majority of instances no significant difference was present in the reaction. Various modifications of Kobrak's technique by Demetriades, Veits, Grahe and Frenzel are in use for the caloric test abroad, the mass douche having been practically abandoned except in this country. An important advance in the technique of studying both spontaneous and induced nystagmus was registered by the introduction of Frenzel's illuminated glasses which eliminate fixation by the patient and at the same time make the observation of the nystagmus much easier for the physician.

The Galvanic Test. The galvanic falling reaction was the subject of study by Blonder and Davis.[6] Using a balance board mounted on a low fulcrum they achieved a refinement of technique which made it possible to obtain a reaction from a patient with very small amounts

of current, generally 0.5 to 2 ma. They tested 100 normal persons as well as a number of pathologic subjects. Of the latter, those with dead labyrinths gave no response even with 10 to 20 ma. of current; varying responses as to the amount of current required were obtained from the others.

Past-pointing. It is now several years since Fischer and Wodak showed that the pointing tests brought out by Bárány are complex reactions in which several elements, besides the vestibular stimulus achieved by the caloric or rotation tests, are of importance. Dorcus and Mowrer[18] made an experimental study of this test following rotation in persons under hypnotic suggestion and on normal subjects who knew that the object to which they were pointing was moving apparently in the same direction as the vertigo. They found past-pointing to be variable. They believe that patients try to correct both for post-rotational vertigo and for the tonic imbalance, which they think is sensed proprioceptively. Better results were obtained with a specially built board where the patient was not asked to point at any specific object, but by grasping certain pendants attached to the board and moving his arms following stimulation made an automatic record on a large sheet of paper which recorded the deviation. In this connection, it should be noted that the drift reaction with the outstretched arms, as elaborated by Wodak, in which the examiner sitting in front of the patient who has his eyes closed "lines up" his outstretched arms at the beginning of the test with those of the patient, is a simple and very sensitive substitute for the past-pointing test.

An investigation of the pointing test was also made by Behrman.[4] He pointed out that the method used for testing had considerable influence upon the result. If the arms are brought up there is a tendency in normal individuals for an outward drift from the midline which is somewhat greater in the right arm; when the arms are brought down no deviation or only a slight inward one is noted. Following stimulation, the drift of the arms is in accord with the principles brought out by Bárány but the degree of the deviation again depends upon the method of stimulation, and is greater when the arms are brought up than when they are brought down. The deviation from calorization gradually increases up to the tenth test and then decreases again gradually. He found that the method of testing determines which arm deviation will be more pronounced. After the cold caloric test the opposite arm deviation is the more pronounced while after warm water irrigation the homolateral one shows a greater drift. Rotation affects the opposite arm (to the rotation) the most. Large quantities of water give greater deviations than small ones and cold water is more effective than hot. The author feels that repeated stimulation tests in the same person give an added value to the pointing test. He found no definite relationship between the onset of dizziness and the degree of past-pointing and none between the direction of the apparent movement (of the vertigo) and that of the deviation. It may be pointed out that the last conclusion is in contradistinction to the teachings of Jones and his school in this country and is in accord with the physiologic principles brought in animal experimentation by Magnus and de Kleijn and in man by Fischer and Wodak indicating that the essential element in past-pointing induced by stimulation is a reflex activity of the musculature of the arms.

Vertigo. The cause of Ménière's symptom complex continues to furnish room for considerable discussion. There is still wide divergence of opinion as to the etiologic factors mainly involved. Eisenberg,[19] for example, studied 33 cases and came to the conclusion that while the condition is not a definite entity and may be due to different diseases, the immediate cause is due to a structural change in the nervous apparatus of the internal ear. Cohen,[13] on the other hand, found headache in all patients suffering from this condition and definite neurologic signs in 9 of his 11 cases. He feels that a primarily neurologic rather than a purely internal ear condition is suggested; in other words, that the cause of the vertigo is central. The borderline between so-called Ménière's symptom complex and attacks of vertigo due to other causes is often ill-defined. In a symposium on vascular disease, Shapiro[47b] gave the following groups of causes for vertigo due to circulatory disturbance:

1. Vasomotor instability without evidence of any structural abnormality in the blood-vessels; this, in his opinion, is the basis for most of the so-called Ménière's syndrome cases. Some of them show hemicranial headache and visual field disturbances at the time of the attack.
2. Blood dyscrasias which may cause vertigo through changes in the internal ear or through deficient oxygenation of the vestibular centers.
3. Circulatory disturbances accompanied by organic changes in the blood-vessels of the internal ear or brain, without or with hypertension, are apt to cause vertigo on change of position because the sclerosed vessels are unable to adjust themselves quickly to the effects of gravity, thus giving rise to a transient cerebral anemia.
4. Cardiac abnormalities with either a retarded or an accelerated pulse with mild cerebral anemia due to deficient heart action.

Two advances have been registered in the treatment of Ménière's syndrome. Furstenberg and his co-workers[22] tested out the theories brought forth some years previously by Dida Dederding on the rôle of disturbances of water balance due to abnormal sodium chloride intake in causing attacks of vertigo. They studied 14 cases of typical Ménière's syndrome which were hospitalized for 30 days or more. These patients were closely observed under various doses of sodium chloride as well as ammonium chloride which causes dehydration. They worked out a diet of which the features were a low content of sodium chloride with calories as needed, as well as considerable protein; vegetables and fruits were so regulated as to approach a neutral reaction from an acid-base standpoint. In addition, relatively large doses of ammonium chloride were administered periodically. This method of treatment gave good results.

Dandy[14] has sectioned the eighth nerve or its vestibular branch in a considerable number of patients suffering from Ménière's syndrome. He feels that the condition is due to some lesion of the nerve rather than in the end organ. The indication is furnished by repeated and intolerable attacks of dizziness with tinnitus and deafness which show no obvious cause and fail to yield to conservative treatment. While the claim of excellent results can no doubt be substantiated in the majority of cases, the Reviewer feels that caution in recommending the measure should be observed even where the presence of tinnitus seems to place the site of the lesion, as peripheral.

Labyrinthitis. The discussion as to the classification and proper methods of handling inflammation of the internal ear secondary to acute or chronic otitis media has occupied otologists for many years. The subject was apparently closed with Ruttin's exhaustive monograph 10 years ago, summarizing the literature and the experiences of the Neumann Clinic at Vienna. There has, however, since that time been noticed a trend towards further conservatism in managing these serious complications. This is emphasized by two important communications. Turner and Fraser[50] observed 216 cases of labyrinthitis in 14,479 cases of otitis media during a period of 25 years. Following Ruttin's classifications their indications for operation are as follows:

(*a*) Circumscribed labyrinthitis—radical mastoidectomy alone or with Hinsberg labyrinth operation if the hearing is poor.

(*b*) Serous labyrinthitis secondary to circumscribed labyrinthitis—radical mastoidectomy alone.

(*c*) Latent labyrinthitis—labyrinth operation at the time of the radical mastoidectomy if the latter is called for, but if the history indicates that the acute labyrinthine symptoms occurred more than 6 months previously, the labyrinth operation may be omitted.

(*d*) Acute serous labyrinthitis—if a simple mastoidectomy is not indicated the patient is put to bed and observed.

(*e*) Acute purulent labyrinthitis—if in the course of a chronic ear infection, a radical mastoidectomy plus the Hinsberg labyrinth operation is done; otherwise the patient is put to bed and watched for rise of temperature or headache.

Lund,[33] following much the same classification, summarized his experience at Copenhagen covering more than 500 cases of labyrinthitis over a period of 28 years. Like the preceding writer, he does not do a labyrinthectomy (as Ruttin indicated) on every case of chronic or latent diffuse labyrinthitis requiring a radical mastoid operation, nor on every patient with acute diffuse suppurative labyrinthitis. He maintains that every case of suppurative labyrinthitis will show a stage of meningeal irritation in the course of intracranial extension. If the patient is seen after a full blown meningitis has developed, labyrinthine operation is generally useless; if he is seen while the process is still confined to the internal ear, repeated observation of the cerebrospinal fluid will furnish the indication for operation. He operates when more than 2 cells per c.mm. are present in the spinal fluid. His statistics indicate that between 1921 and 1935 when these indications were followed for acute diffuse suppurative labyrinthitis is the best record—a mortality of only 31% of the entire period covered by the study was achieved.

Central Vestibular Disturbances. Nylen,[42] who previously studied spontaneous and positional nystagmus in a large group of brain tumors, reports on the symptomatology, from the vestibular standpoint, of experimentally induced brain tumors. He introduced into the cranial cavities of rabbits and rats laminaria tents or a small amount of Jensen's sarcoma, the former to cause a rapid, the latter a slow increase of intracranial pressure. He produced abnormal eye displacements, nystagmus and positional nystagmus which were manifested regardless of the location of the tumor, but were more marked when it was close to or in contact with the vestibular centers. The nystagmus was still present after destruction of both labyrinths; either the horizontal, rotatory or vertical form could be seen. The practical significance of the

above study is to indicate in an experimental way the possible effect of remote tumors and other pressure-producing conditions within the cranial cavity upon the vestibular centers. This fact must always be borne in mind when attempting localization of tumors from vestibular symptoms.

A comprehensive study upon the relation of the frontal lobe to equilibrium is contributed by Delmas-Marsalet.[15] The report is of interest here as it tends to corroborate the cerebellar and vestibular connections which have been previously dwelt upon by Goldstein and others. Delmas-Marsalet indicates the existence of a connection between the prefrontal lobe and the crossed cerebellar hemisphere and between the prefrontal lobe and the homolateral vestibular nerve. He states that the frontal lobe appears to be a postural center for the neck and trunk. Disturbances of coördination due to frontal lobe lesions are rich in symptomatology but can be grouped under four heads: cerebellar, labyrinthine, prexic and gnostic. The labyrinthine symptoms are inclinations of the head and body toward the lesion, spontaneous past-pointing and deviation of the gait both toward the lesion. Various combinations of symptoms can occur and many frontal lobe lesions show no disturbances of coördination. He believes that the vestibular impulses probably reach the frontal lobe by way of the globus pallidus.

Beilin[5] studied the posture of the head in 12 cases of cerebello-pontine angle tumor all of whom but 1 had originated from the acoustic nerve. After discussing the various theories, Beilin came to the conclusion that as the head was turned in each case towards the side of the lesion the symptoms must be due to irritation of the vestibular centers in the brain.

Disturbances of Hearing Due to Central Lesions. A considerable increase in the number of clinical reports bearing upon this question has been noted within the past few years. Lawson[30] reported a tumor of the midbrain, extending partly into the left hemisphere, in which there was a hearing loss of about 12% in the right ear and about 60% in the left. Autopsy and previous examination revealed no other cause for the deaness. The finding of a homolateral deafness is not in accord with the teachings of observers abroad, such as Ruttin and Grahe, who indicated the loss to be either approximately equal on each side or more pronounced on the contralateral side—a finding which would be expected from the fact that most of the fibers which enter the brain stem, eventually cross to the opposite side. This thought is supported by the findings of Kompaneets,[28] who studied the hearing in 5 patients that had recovered from temporal lobe abscess. Both bone and air conduction were found to be reduced on the contralateral ear but chiefly for the low tones; hearing for conversations was not impaired. It must be said that most American observers have not been able to bring out the existence of central deafness. Neither Northington[41] nor McNally *et al.*,[36] in their study of brain tumors, could establish that deafness existed in these conditions excepting the ones involving the eighth nerve or the cerebello-pointine angle.

A notable contribution to this field is made by Brunner[9] on the basis of his experience and autopsies over fifteen years. He first disposed of the question as to whether a condition of stasis in the internal ear can occur analogous to the choking of the optic disk which is seen in increased intracranial pressure. He believes that this condition does not occur in consequence of a generalized intracranial hypertension but does occur at times in cerebello-pontine angle tumors as a result

of compression of the two veins which carry the return flow from the internal ear. Relief of pressure in these circumstances will cause a return of the hearing (this has been noted by the Reviewer). Besides acusticus and cerebello-pontine angle tumors, tumors of the midbrain can cause deafness. This was first noted by Siebenmann. The hearing loss may be unilateral due to interruption of the contralateral pathway, or bilateral due to destruction of both secondary auditory pathways. Characteristically differentiating it from acusticus and cerebello-pontine tumor deafness is the hyperactive labyrinth which is present. Cerebellar tumors may also occasionally cause deafness. Brunner feels that, although the hearing center is definitely located in the cortex of the temporal lobe, it cannot be said that the existence of deafness due to tumors in this area is established.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF APRIL 18, 1938

Investigation of the Blood-vessels of the Finger by the Method of Pressure Analysis. ALAN C. BURTON (Eldridge Reeves Johnson Foundation, University of Pennsylvania). Observations upon the changes of the finger volume pulse when external pressure is applied to the finger may give information as to the reactions of the vessels of different categories of the vascular tree. Though indirect, the evidence so obtained is statistical for all vessels present of a given class, while in the more direct methods only a few representative vessels can be observed.

The pressure within a plethysmographic cuff placed on the middle phalanx is quickly raised above systolic pressure and allowed to fall steadily to zero while the pulsations of finger volume are recorded photographically by a mirror oscillometer. From the record the amplitude of pulsation is then plotted against the pressure in the plethysmograph.

Similar procedure on a single artery gives a characteristic pulsation-pressure curve with a single maximum at about the diastolic pressure, determined by application of the various diastolic criteria to the wave form. The finger, however, gives curves showing several peaks of variable height but fairly constant occurrence. The various curves can, in general, be analyzed as made up of 5 components, which are tentatively associated with different groups of vessels, namely the veins, the capillaries, arterioles, arterial network and digital arteries. Changes of wave form and diastolic criteria seen to apply at more than one pressure suggest the progressive shifting of the origin of the pulsation as the cuff pressure falls.

Changes in the height and position of the component peaks of pulsation with reflex constriction and dilation and their position in the hypertensive are consistent with this interpretation.

Confirmation is found in the decreases of finger volume as the cuff pressure is steadily raised. These occur in discrete steps at pressures which coincide with the 5 component peaks of pulsation.

Respiratory Transport by the Blood of Some Fresh Water Fish. E. C. BLACK and LAURENCE IRVING (Martin Biological Laboratory, Swarthmore College). On account of the natural variations in pressure of O_2 and CO_2 in fresh water with place, depth, and season, environmental conditions for the respiration of fish differ from the constant conditions in air. The average O_2 capacity of blood of the carp at 15° is, 13.1 c.cm. per 100 c.cm., of corpuscles 41 c cm.; of the sucker, 10.4 c.cm. for blood, 35 c.cm. for corpuscles.

The curves relating O_2 content to O_2 pressure are not sigmoid but hyperbolic in form. CO_2 at small pressures reduces the O_2 capacity and prevents saturation even at O_2 pressures of 200 mm. In the blood of carp, the pressure of O_2 necessary for 50% saturation is increased by 1 mm. for each mm. pressure of CO_2. In the sucker, 1 mm. CO_2 raises the pressure of O_2 for half saturation by 6.0 mm. The CO_2 effect is reversible.

Changes in pressure of CO_2 are more important in O_2 transport than in mammalian blood in which at 50% saturation 3.5 mm. CO_2 increases O_2 pressure by only 1 mm., and the observed variations of CO_2 in natural waters would determine the possibility of respiration of these fish.

The CO_2 effect differs from the Haldane effect in mammalian blood. In the fish blood, acid causes anomalous swelling of corpuscles, fluoride and oxalate diminish the CO_2 effect, and hemolysis with saponin destroys the CO_2 effect. It seems attributable to a membrane or permeability condition which influences the hemoglobin by changing the ions within the corpuscle.

The Diabetogenic Action of the Anterior Pituitary. EVERETT IDRIS EVANS (Laboratory of Physiology, University of Chicago). Studies have now been completed on 24 normal and 7 "Houssay" dogs. Diabetogenic extracts have been made, using the extraction of beef anterior pituitary by strong alkali, in the cold. It has been possible to produce marked diabetogenic effects in 16 normal dogs and in each of the Houssay animals; 8 normal dogs proved refractive.

Data are now available on the effect of this extract on the blood sugar, total lipoids, pH and total CO_2, urine sugar, urine volume and glucose tolerance, of normal dogs. The blood sugar (fasting) rises to 160 to 533 mg. % in 4 to 5 days, stays elevated for about 5 days, to return sharply to a subnormal level on about the 10th to 12th day. The subnormal level (35 to 70 mg. %) is maintained for 4 to 6 days.

The total lipoids of the blood may rise to 9.5% on a low fat intake. The usual level is about 1.5 to 2.5%. On the 5th to 6th day, when the blood sugar is high (400–500 mg. %), the pH may fall to 7.35 and the total CO_2 to 30 vol. % and the acidosis may have to be relieved by insulin and alkalies.

In certain animals, the sugar output in the urine may rise to 45–55 gm. daily at the peak of the hyperglycemia, with the animals on a low sugar intake. Polyuria and polydipsia was noted in all 16 affected animals. Death in coma resulted in 2 animals with marked, untreated hyperglycemia.

Marked diabetogenic activity was found on injection of highly purified Prolactin (33 units/mg.) in doses of 0.4 and 1.0 mg./kilo in 2 Houssay dogs.

It is evident that normal dogs after 25 to 30 days of injections, with fasting normal blood sugars, show markedly abnormal glucose tolerance curves. They may be said to be in a "pre-diabetic" state. This agrees well with the findings of Young, on the production of a permanent diabetes with anterior pituitary extracts.

Correction. In the article by John B. Youmans and Marvin B. Corlette on "Specific Dermatoses Due to Vitamin A Deficiency" appearing in the preceding issue of this JOURNAL (May, p. 644) Figures 3 and 5 have been interchanged. Figure 3 should designate "after" treatment and Figure 5 "before" treatment. EDITORS.

NOTE ON ARTICLE ON "RUBBER SHEATHS AS VENEREAL DISEASE PROPHYLACTICS: THE RELATION OF QUALITY AND TECHNIQUE TO THEIR EFFECTIVENESS." (*Am. J. Med. Sci.*, **195**, 155, 1938.)

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INDEX.

A

Abbott, W. O., Zetzel, L., and Glenn, P. M., observations on motor activity of obstructed small intestine in treatment by intubation, 279
Acetyl-beta-methycholine chloride, effect of iontophoresis with, on rate of peripheral blood flow, 794
Acidity, gastric, control of, in peptic ulcer by alkalinized powdered skim milk tablets, 676
Acromegaly and diabetes mellitus, case of xanthoma diabeticorum associated with, 50
Addiction, our new; marihuana, 351
Addison, W. H. F., *see* Comroe, J. H., Jr., 715
Adolph, P. E., and Lockwood, J. S. sulphanilamide in experimental streptococcic meningitis, 575
Adrenal cortex, relation of, to experimental diabetes, 277
(Agranulocytosis) neutropenia, etiologic importance of fatigue and prognostic significance of monocytosis in, 627
Alcohol, sterility of, 358
  tobacco amblyopia, treatment of, 274
Alkalinized powdered skimmed milk tablets, control of gastric acidity in peptic ulcer by, 676
Alsted, G., Minot, G. R., and Pohle, F. J., *see* Heath, C. W., 281
Altshuler, S. S., and Leiser, R., effect of zinc content upon action of insulins, 234
Amblyopia, tobacco alcohol, treatment of, 274
Amyloidosis, evacuation of Congo-red test for; autopsy findings and dye absorption in 125 cases, 205
Anderson, H. H., and Soley, M. H., effects on carotenemia on function of thyroid and liver, 313
Anemia, hypochromic, influence of mucin upon absorption of iron in, 281
  influence of, on blood sedimentation, 734
  macrocytic, in cancer of stomach, apparently due to lack of intrinsic factor, 17
  pernicious, observations on 78 cases of, with special reference to weight changes, 150
  opticatrophy in, 633
Anterior pituitary, diabetogenic action of, 851
Aorta of dog, peculiar form of medial calcification in, 47
Aortic chemoreceptors, significance of, in dog, 715
Appelbaum, E., *see* Neal, J. B., 175
Appendicitis, acute, and lucid interval, 529
Armstrong, H. G., blood pressure and pulse rate as index of emotional stability, 211
Arrhythmia, cardiac, characteristic effect of thiobarbiturates, as influenced by changes in arterial blood pressure, 575
Arterial blood pressure, cardiac arrhythmia, characteristic effect of thiobarbiturates, as influenced by changes in, 575
Arteriosclerosis, gross, course of hypertensive heart disease, in relation to, 638
Asher, D. W., and Foster, C., *see* Church, C. F., 714
Asthma, bronchial, subcutaneous emphysema complicating; case report and 17 previous ones, 682
Atrophy, optic, in pernicious anemia, 633
Atropine therapy, high dosage, in chronic encephalitic parkinsonism, 809
Austin, B. R., *see* Ketteringham, R. C., 318
Autonomic pharmacology, human, VII, 88

B

Bachmann, R. A., note on rubber sheaths as venereal disease prophylactics, 852
Bacteria, acid-fast, intracutaneous reactions in man to purified protein derivatives of, 479
Baine, J. O., *see* Gettler, A. O., 182
Barker, W. H., and Miller, D. K., clinical observations on Whipple liver fraction (secondary anemia fraction), 287
Basal metabolic rate of children with Sydenham's chorea; 42 patients, 519
Beck, L. V., and Richards, A. N., action of cyanide and of oxygen lack on glomerular function in perfused frog's kidney, 714
Beebe, G. W., and Dickinson, R. L., *see* Cautley, R., 155
Beerman, H., and Ingraham, N. R., Jr., *see* Stokes, J. H., 562
Benjamin, J. E., Landt, H., and Culver, L. R., body as volume conductor and influence on electrical field of heart, 759
Benzedrine sulphate, effect of, on bowel and uterus, 445

Benzedrine sulphate, symptomatic treatment of chronic encephalitis with, 448
Beta hemolytic streptococcic infections, sulphanilamide in treatment of, 163
Bing, J., and Nørgaard, F., *see* Petri, S., 717
Black, E. C., and Irving, L., respiratory transport by blood of fresh water fish, 850
Blake, F. G., *see* Hageman, P. O., 163
Block, F. B., ectopic pregnancy, 553
Blood and urine of dogs following paraldehyde, 329
cells of fetal rat, effect on, by inhalation of carbon tetrachloride by mother during gestation, 787
cultures after tonsillectomy, 667
flow, peripheral, effect of iontophoresis with acetyl-beta-methylcholine chloride, on rate of, 794
from normal human subjects, spectrographic determination of lead in, 622
lipids, changes in, during insulin treatment of schizophrenia, 802
of fresh water fish, respiratory transport by, 850
pressure and blood volume, studies in, following extravascular administration of fluid in rats, 137
pulse rate as index of emotional stability, 211
skin temperature of rabbit's ear, effects of pressor drugs and saline kidney extracts on, 427
proteins, studies of, in delirium tremens, 820
sedimentation, influence of anemia on, 734
serial, and bone-marrow findings of 8-month premature, and Roentgen ray treated chronic myeloid leukemic mother, 8
sugar during labor, at delivery and post-partum, with observations on newborns, 318
vessels of finger, investigation of, by pressure analysis, 850
volume and blood pressure, studies in, following extravascular administration of fluid in rats, 137
Bloomfield, A. L., natural history of chronic hepatitis (cirrhosis of liver), 429
Body as volume conductor and influence on electrical field of heart, 759
Bone, human, composition of, in chronic fluoride poisoning, 493
marrow and serial blood findings of 8-month premature, and Roentgen ray treated chronic, myeloid, leukemic mother, 8
Bone marrow, human, culture of: improved apparatus for large scale culture, 141
splenogenic controlling of cell emission from, and tuberculous splenomegaly, study of, 32
Boone, J. A., and Levine, S. A., prognosis in "potential rheumatic heart disease" and "rheumatic mitral insufficiency," 764
Bowel and uterus, effect of benzedrine sulphate on, 445
Bower, J. O., lucid interval and acute appendicitis, 529
Boyd, E. M., effect of benzedrine sulphate on bowel and uterus, 445
Breast, carcinoma of, further note on, in one of homologous twin sisters, 366
Briese, E., effect on blood cell of fetal rat by inhalation of carbon tetrachloride by mother during gestation, 787
Bronchial asthma, subcutaneous emphysema complicating; case report and 17 previous ones, 682
Buchanan, J. A., and Indelicato, J. C., case of xanthoma diabeticorum associated with diabetes mellitus and acromegaly, 50
Bumbalo, T. S., *see* Jetter, W. W., 362
Burkhardt, E. A., Eggleston, C., and Smith, L. W., electrocardiographic changes and peripheral nerve palsies in toxic diphtheria, 301
Burton, A. C., investigation of blood-vessels of finger by method of pressure analysis, 850
Burwell, C. S., placenta as modified arteriovenous fistula; relation to circulatory adjustments to pregnancy, 1
Butt, E. M., *see* Thienes, C. H., 522

C

Calcification, medial, peculiar form of, in aorta of dog, 47
Cameron, D. E., and Looney, J. M., *see* Randall, L. O., 802
Campbell, R., *see* Griffith, J. Q., Jr., 137
Cancer of colon, 267
stomach, macrocytic anemia in, apparently due to lack of intrinsic factor, 17
Carbohydrate and water metabolism and vitamins in skin inflammation (dermatitis), 562
Carbon tetrachloride, effect on blood cells of fetal rat by inhalation of, by mother during gestation, 787
Carcinoma of breast, further note on, in one of homologous twin sisters, 366
Cardiovascular complications of hyperthyroidism, 248
syphilis, occult, 240
Carotenemia, effects of, on function of thyroid and liver, 313

Cautley, R., Beebe, G. W., and Dickinson, R. L., rubber sheaths as venereal disease prophylactics; quality and technique, 155
Cell emission from bone marrow, study of tuberculous splenomegaly and splenogenic controlling of, 32
Cerebral circulation, action of chemical substances on, 427
cortex, conduction of labyrinthine impulses to, 138
Cervical nerves, rôle of, in facial sensations, 576
Chemical substances, action of, on cerebral circulation, 427
Chemoreceptors, aortic, significance of, in dog, 715
Chemotherapy, sulphanilamide and similar compounds in, 379
Chemotropism of leukocytes, effect of prontosil and related compounds upon, 574
Childhood, tuberculosis in, 129
Children with Sydenham's chorea, basal metabolic rate of; 42 patients, 519
Choline compounds, effects of, in neurologic disorders, with reference to Ménière's syndrome, 83
Chorea, Sydenham's relationship of, to other rheumatic manifestations, 656
Church, C. F., Foster, C., and Asher, D. W., effect of diet upon host resistance to enteritidis infection, 714
Cinchophen, acquired sensitivity to; 6 case reports and review, 473
Circulatory, chronic, effects of tobacco and nicotine of, 522
(Cirrhosis of liver) chronic hepatitis, natural history of, 429
Climate and season, influence of, on mortality of white and colored population from tuberculosis and respiratory infections, 501
Cole, V. V., and Harned, B. K., glucose tolerance in normal rats, 138
see Harned, B. K., 138
Colon, cancer of, 267
motility and defecation in dog, influence of filling stomach on, 230
Colored and white population, influence of season and climate on mortality of, from tuberculosis and respiratory infections, 501
Coman, D. R., effect of prontosil and related compounds on chemotropism of leukocytes, 574
Comroe, J. H., Jr., and Addison, W. H. F., localization and physiological significance of aortic chemoreceptors in dog, 715
Congo-red test for amyloidosis, evaluation of; autopsy findings and dye absorption in 125 cases, 205
Connor, R., and Fields, H., *see* Sunderman, F. W., 469
Cooper, M. J., effects of choline compounds in neurologic disorders, with reference to Ménière's syndrome, 83
Corlette, M. B., *see* Youmans, J. B., 644
Youmans, J. B., Frank H., and Corlette, M. G., photometric studies of visual adaptation in relation to mild vitamin A deficiency in adults, 54
Corlette, M. G., Youmans, J. B., and Frank H., *see* Corlette, M. B., 54
Coronary thrombosis, cause of death in, with reference to pulmonary embolism, 104
Corwin, W. C., and Cragg, R. W., peculiar form of medial calcification in aorta of dog, 47
Cragg, R. W., *see* Corwin, W. C., 47
Creatine tolerance test in differential diagnosis of Graves' disease, etc., 608
Culture of human marrow: improved apparatus for large scale culture, 141
Culver, L. R., and Landt, H., *see* Benjamin, J. E., 759
Custer, R. P., experimental pathology of ergotism; some newer ergot derivatives, 452
Cutler, J. W., Park, F. R., and Herr, B. S., influence of anemia on blood sedimentation, 734
Cyanide, action of, and of oxygen lack on glomerular function in frog's kidney, 714
toxicology of, 182
Czarnetzky, E. J., and Sevag, M. G., action of sodium bisulphite and sulphanilamide on purine and pyrimidine compounds, etc., 426

D

Dameshek, W., Loman, J., and Myerson, A., human autonomic pharmacology, VII, 88
Death, cause of, in coronary thrombosis, with reference to pulmonary embolism, 104
Defandorf, J. H., blood and urine of dogs following paraldehyde, 329
Delirium tremens, studies of blood proteins in, 820
(Dermatitis) skin inflammation, carbohydrate and water metabolism and vitamin in, 562
Dermatoses, specific, due to vitamin A deficiency, 644
Diabetes, experimental, relation of adrenal cortex to, 277
mellitus and acromegaly, case of xanthoma diabeticorum associated with, 50
studies in, VI. Mortality and longevity of diabetics, 596
Diabetic patient, obese, dietary *versus* insulin treatment of, 781

Diabetogenic action of anterior pituitary, 851
Diastolic hypertension, recent concepts in pathogenesis of, 115
Diazomethane poisoning; first clinical case report, 469
Dickinson, R. L., and Beebe, G. W., *see* Cautley, R., 155
Diet, effect of, upon host resistance to enteritidis infection, 714
manipulation of glucose tolerance by, 773
Dietary *versus* insulin treatment of obese diabetic patient, 781
Diphtheria, toxic, electrocardiographic changes and peripheral nerve palsies in, 301
Diphtheriology, some recent advances in, 417
Direct method, normal venous pressure as determined by, 751
Diuresis, water, experiments on, 715
Dodge, K. G., *see* Sutton, L. P., 656
Dohan, F. C., and Lukens, F. D. W., observations on relation of adrenal cortex to experimental diabetes, 277
Dozzi, D. L., transient nodal rhythm following use of sulphanilamide, 771
Dublin, L. I., and Marks, H. H., *see* Joslin, E. P., 596
Duncan, G. G., and Durkin, J. K., *see* Fetter, F., 781
Durkin, J. K., and Duncan, G. G., *see* Fetter, F., 781

E

Ebaugh, F. G., psychiatric facilities in general hospital, 833
Ectoderm, explanted gastrular, effect of dead optic vesicle on, 574
Ectopic pregnancy, 553
Eggleston, C., and Smith, L. W., *see* Burkhardt, E. A., 301
Electrocardiographic changes and peripheral nerve palsies in toxic diphtheria, 301
Emotional stability, blood pressure and pulse rate as index of, 211
Emphysema, subcutaneous, complicating bronchial asthma; case report and 17 previous ones, 682
Encephalitic parkinsonism, chronic, high-dosage atropine therapy in, 809
Encephalitis, chronic, symptomatic treatment of, with benzedrine sulphate, 448
Engelbreth-Holm, J., study of tuberculous splenomegaly and splenogenic controlling of cell emission from bone marrow, 32
Enteritidis infection, effect of diet upon host resistance to, 714
Eosinophil, etiologic relation of, to Gordon phenomenon in Hodgkin's disease, 27
Eppinger, E. C., and Kennedy, J. A., cause of death in coronary thrombosis, with reference to pulmonary embolism, 104
Erf, L. A., studies of Gaucher cells by supravital technique, 144
and Fine, A., serial blood and bone-marrow findings of 8-month premature, and Roentgen ray treated chronic, myeloid leukemic mother, 8
Ergonovine *versus* ergotamine as terminator to migraine headaches, 458
Ergotamine, ergonovine *versus*, as terminator of migraine headaches, 458
Ergotism, experimental pathology of; some newer ergot derivatives, 452
Ernstene, A. C., cardiovascular complications of hyperthyroidism, 248
Erythrocyte; photographic recorder of suspension stability of; sedimentometer, 729
Essential hypertension in negro, 510
Etiology of toxemias of pregnancy, III, 516; IV, 723
Evans, E. I., diabetogenic action of anterior pituitary, 851
Extravascular administration of fluid in rats, studies in blood volume and blood pressure following, 137

F

Facial sensations, rôle of cervical nerves in, 576
Falconer, E. H., and Leonard, M. E., pulmonary involvement in lymphosarcoma and lymphatic leukemia, 294
Farr, L. E., assimilation of protein by young children with nephrotic syndrome, 70
Fatigue, etiologic importance of, and prognostic significance of monocytosis in neutropenia (agranulocytosis), 627
Feldman, W. H., *see* Stasney, J., 20
Fels, S. S., and Gershon-Cohen, J., *see* Shay, H., 139
Fetter, F., Durkin, J. K., and Duncan, G. G., dietary *versus* insulin treatment of obese diabetic patient, 781
Fields, H., and Connor, R., *see* Sunderman, F. W., 469
Fine, A., *see* Erf, L. A., 8
Finger, investigation of blood-vessels of, by pressure analysis, 850
Fish, fresh water, blood of, respiratory transport by, 850
tumors of peripheral nerves in, 278
Flake, C. G., *see* Southworth, H., 667
Flaxman, N., course of hypertensive heart disease; in relation to gross arteriosclerosis, 638
Fluoride poisoning, chronic, composition of human bone in, 493
Foster, C., and Asher, D. W., *see* Church, C. F., 714

Frank, H., Youmans, J. B., and Corlette, M. G., *see* Corlette, M. B., 54
Frank, I. L., and Ravdin, I. S., *see* Thompson, W. D., Jr., 426
Friedland, C. K., and Hollings, H. E., *see* Montgomery, H., 794
Frobisher, M., Jr., some recent advances in diphtheriology, 417

G

Galapeaux, E. A., and Templeton, R. D., influence of filling stomach on colon motility and defecation in dog, 230
Gastrectomy in young swine, pathological changes produced by, 717
Gastric acidity after gastro-enterostomy, 220
control of, in peptic ulcer by alkalinized powdered skimmed milk tablets, 676
secretion, rôle of upper small intestine in control of, etc., 139
Gastritis, chronic, 708
Gastro-enterostomy, gastric acidity after, 220
Gaucher cells, studies of, by supravital technique, 144
Gershenfeld, L., sterility of alcohol, 358
Gershon-Cohen, J., and Fels, S. S., *see* Shay, H., 139
Gestation, effect on blood cells of fetal rat by inhalation of carbon tetrachloride by mother during, 787
Gettler, A. O., and Baine, J. O., toxicology of cyanide, 182
Getz, H. R., and Stiehm, R. H., *see* McCarter, J., 479
Glenn, P. M., and Zetzel, L., *see* Abbott, W. O., 279
Glomerular function in frog's kidney, action of cyanide and of oxygen lack on, 714
Glucose tolerance in normal rats, 138
manipulation of, by diet, 773
Goldhamer, S. M., macrocytic anemia in cancer of stomach, apparently due to lack of intrinsic factor, 17
Gordon phenomenon, etiologic relation of eosinophil to, in Hodgkin's disease, 27
Graves' disease, etc., creatine tolerance test in differential diagnosis of, 608
Greene, J. A., coexistence of myxedema and pellagra in same patient; 2 case reports, 618
Griffith, J. Q., Jr., and Campbell, R., studies in blood volume and blood pressure following extravascular administration of fluid in rats, 137
Gruber, C. M., Haury, V. G., and Gruber, C. M., Jr., cardiac arrhythmia, characteristic effect of thiobarbiturates, as influenced by changes in arterial blood pressure, 575
Gruber, C. M., Jr., and Haury, V. C., *see* Gruber, C. M., 575

H

Hageman, P. O., purulent typhoid meningitis with recovery; case report, 497
Hageman, P. O., and Blake, F. G., sulphanilamide in treatment of beta hemolytic streptococcic infections, 163
Harned, B. K., and Cole, V. V., hyperglycemia produced by synergistic action of strychnine and physostigmine, 138
see Cole, V. V., 138
Harrison, T. R., and Mason, M. F., *see* Williams, J. R., Jr., 339
Hartline, H. K., origin of "off" response in optic pathway, 279
Haury, V. G., and Gruber, C. M., Jr., *see* Gruber, C. M., 575
Headaches, migraine, ergonovine *versus* ergotamine as terminator of, 458
Heart disease, hypertensive, course of; in relation to gross arteriosclerosis, 638
potential rheumatic, and "rheumatic mitral insufficiency," prognosis in, 764
electrical field of, body as volume conductor and influence on, 759
Heath, C. W., Minot, G. R., Pohle, F. J., and Alsted, G., influence of mucin upon absorption of iron in hypochromic anemia, 281
Hemolytic streptococci, invasive properties of, and their control by sulphanilamide, 577
Hendrix, J. P., *see* Schmidt, C. F., 427
Hepatitis, chronic (cirrhosis of liver), natural history of, 429
Hepatosplenography, histopathologic study of tissues of 65 patients injected with thorium dioxide sol for, 198
Herr, B. S., and Park, F. R., *see* Cutler, J. W., 734
Hodgkin's disease, etiologic relation of eosinophil to Gordon phenomenon in, 27
Holbrook, A. A., normal venous pressure as determined by direct method, 751
Hollings, H. E., and Friedland, C. K., *see* Montgomery, H., 794
Holman, C., and Sandusky, W. R., gastric acidity after gastro-enterostomy, 220
Holmes, S. J., influence of season and climate on mortality of white and colored population from tuberculosis and respiratory infections, 501
Hospital, general, psychiatric facilities in, 833
Human autonomic pharmacology, VII, 88

Human marrow, culture of: an improved apparatus for large scale culture, 141
Hydrocephalus, post-traumatic internal, 65
Hyperglycemia produced by synergistic action of strychnine and physostigmine, 138
Hypertension, diastolic, recent concepts in pathogenesis of, 115
Hypertension, essential, in negro, 510
Hyperthyroidism, cardiovascular complications of, 248
Hypoproteinemia, correcting, and preventing wound disruption, use of lyophile plasma in, 426

I

INDELICATO, J. C., *see* Buchanan, J. A., 50
Infection, enteritidis, effect of diet upon host resistance to, 714
Infections, beta hemolytic streptococcic, sulphanilamide in treatment of, 163
various, use of sulphanilamide in treatment of, 701
Ingraham, N. R., Jr., and Beerman, H., *see* Stokes, J. H., 562
Insulin treatment of schizophrenia, changes in blood lipids during, 802
versus dietary treatment of obese diabetic patient, 781
Insulins, effect of zinc contents upon action of, 234
Intestine, small, obstructed, motor activity of, in treatment by intubation, 279
upper small, rôle of, in control of gastric secretion, etc., 139
Intracranial pressure and oxygen want, 673
Intracutaneous reactions in man, comparison of, to purified protein derivatives of acid-fast bacteria, 479
Intrinsic factor, lack of, macrocytic anemia in cancer of stomach, apparently due to, 17
Intubation, motor activity of obstructed small intestine in treatment by, 279
Iontophoresis, effect of, with acetyl-beta-methylcholine chloride on rate of peripheral blood flow, 794
Iron, influence of mucin upon absorption of, in hypochromic anemia, 281
Irving, L., *see* Black, E. C., 850
Ivy poisoning, experimental, negative results of Rhus antigen treatment of, 361

J

JACKSON, H., JR., and Parker, F., Jr., *see* Turner, J. C., 27
Jetter, W. W., and Bumbalo, T. S., urinary output of vitamin C in active tuberculosis in children, 362
Jewett, S. P., Rosow, H. M., and Pumpian-Mindlin, E., high-dosage atropine therapy in chronic encephalitic parkinsonism, 809
Johnston, C. G., *see* Ravdin, I. S., 267
Johnston, C. R. K., *see* McCullagh, E. P., 773
Jones, E., observations on 78 cases of pernicious anemia with special reference to weight changes, 150
see Kampmeier, R. H., 633
Joslin, E. P., Dublin, L. I., and Marks, H. H., studies in diabetes mellitus, VI. Mortality and longevity of diabetics, 596

K

KAMPMEIER, R. H., and Jones, E., optic atrophy in pernicious enemia, 633
Kaplan, I. I., further note on carcinoma of breast in one of homologous twin sisters, 366
Keefer, C. S., use of sulphanilamide in treatment of various infections, 701
Kennedy, J. A., *see* Eppinger, E. C., 104
Kerr, E. G., *see* Wolff, W. A., 493
Ketteringham, R. C., and Austin, B. R., blood sugar during labor at delivery and post-partum, with observations on newborns, 318
King, F. H., and Reiner, M., *see* Sohval, A. R., 608

L

LABOR, blood sugar during, at delivery and post-partum, with observations on newborns, 318
Labyrinthine impulses, conduction of, to cerebral cortex, 138
Landis, E. M., Montgomery, H., and Sparkman, D., effects of pressor drugs and of saline kidney extracts on blood pressure and skin temperature of rabbit's ear, 427
Landt, H., and Culver, L. R., *see* Benjamin, J. E., 759
Lead, spectrographic determination of, in blood from normal human subjects, 622
Lee, T., sedimentometer; photographic recorder of suspension stability of erythrocytes, 729
Leiser, R., *see* Altshuler, S. S., 234
Lennox, W. G., ergonovine *versus* ergotamine as terminator of migraine headaches, 458
Leonard, M. E., *see* Falconer, E. H., 294
Leukemia, lymphatic, and lymphosarcoma, pulmonary involvement in, 294
Leukemic, chronic myeloid, mother, Roentgen ray treated, and 8-month premature, serial blood and bone-marrow findings of, 8

Leukocytes, chemotropism of, effect of prontosil and related compounds upon, 574
Leukocytic response, character of, to tuberculin in sensitized calves, 20
Levine, S. A., *see* Boone, J. A., 764
Lewy, F. H., rôle of cervical nerves in facial sensations, 576
Lipstein, S., evaluation of Congo-red test for amyloidosis; autopsy findings and dye absorption in 125 cases, 205
Liver and thyroid, effects of carotenemia on function of, 313
(Liver, cirrhosis of) chronic hepatitis, natural history of, 429
fraction, Whipple (secondary anemia fraction), clinical observations on, 287
Lockwood, J. S., *see* Adolph, P. E., 575
Loman, J., and Myerson, A., *see* Dameshek, W., 88
Longcope, W. T., invasive properties of hemolytic streptococci and their control by sulphanilamide, 577
Looney, J. M., and Cameron, D. E., *see* Randall, L. O., 802
Lucké, B., tumors of peripheral nerves in fish, 278
Lueth, H. C., basal metabolic rate of children with Sydenham's chorea; 42 patients, 519
Lukens, F. D. W., *see* Dohan, F. C., 277
Lymphosarcoma and lymphatic leukemia, pulmonary involvement in, 294
Lyophile plasma, use of, in correcting hypoproteinemia and preventing wound disruption, 426

M

McCarter, J., Getz, H. R., and Stiehm, R. H., intracutaneous reactions in man to purified protein derivatives of acid-fast bacteria, 479
McCullagh, E. P., and Johnston, C. R. K., manipulation of glucose tolerance by diet, 773
McMillen, J. H., *see* Scott, G. H., 622
Marihuana; our new addiction, 351
Marks, H. H., and Dublin, L. I., *see* Joslin, E. P., 596
Marrow, *see* Bone marrow, 141
Mason, M. F., and Harrison, T. R., *see* Williams, J. R., Jr., 339
Matthews, R. A., symptomatic treatment of chronic encephalitis with benzedrine sulphate, 448
Medial calcification, peculiar form of, in aorta of dog, 47
Ménière's syndrome, effects of choline compounds in neurologic disorders, with reference to, 83
Meningitis, experience with sulphanilamide in, 175
Meningitis, experimental streptococcic, sulphanilamide in, 575
purulent typhoid, with recovery; case report, 497
Michelson, J., and Thompson, J. W., oxygen want and intracranial pressure, 673
Migraine headaches, ergonovine *versus* ergotamine as terminator of, 458
Milk tablets, alkalinized powdered skimmed, control of gastric acidity in peptic ulcer by, 676
Miller, D. K., *see* Barker, W. H., 287
Minot, G. R., Pohle, F. J., and Alsted, G., *see* Heath, C. W., 281
"Mitral insufficiency, rheumatic," and "potential rheumatic heart disease," prognosis in, 764
Monocytosis in neutropenia (agranulocytosis), etiologic importance of fatigue and prognostic significance of, 627
Montgomery, H., and Sparkman, D., *see* Landis, E. M., 427
Hollings, H. E., and Friedland, C. K., effect of iontophoresis with acetyl-beta-methylcholine chloride on rate of peripheral blood flow, 794
Moritz, A. R., and Wartman, W. B., post-traumatic internal hydrocephalus, 65
Motor activity of obstructed small intestine in treatment by intubation, 279
Mucin, influence of, upon absorption of iron in hypochromic anemia, 281
Myerson, A., and Loman, J., *see* Dameshek, W., 88
Myxedema and pellagra, coexistence of, in same patient; 2 case reports, 618

N

Neal, N. B., and Appelbaum, E., experience with sulphanilamide in meningitis, 175
Negro, essential hypertension in, 510
Nephrotic syndrome, assimilation of protein by young children with, 70
Nerve palsies, peripheral, and electrocardiographic changes in toxic diphtheria, 301
Nerves, cervical, rôle of, in facial sensations, 576
peripheral, tumors of, in fish, 278
Neurologic disorders, effects of choline compounds in, with reference to Ménière's syndrome, 83
Neutropenia (agranulocytosis), etiologic importance of fatigue and prognostic significance of monocytosis in, 627
Newborns, blood sugar during labor, at delivery and post-partum, with observations on, 318

Nicotine and tobacco, chronic circulatory effects of, 522
Nodal rhythm, transient, following use of sulphanilamide, 771
Nørgaard, F., and Bing, J., *see* Petri, S., 717

O

"Off" response, origin of, in optic pathway, 279
Optic atrophy in pernicious anemia, 633
pathway, origin of "off" response in, 279
Optic vesicle, dead, effect of, on explanted gastrular ectoderm, 574
Osgood, E. E., culture of human marrow: improved apparatus for large scale culture, 141
Otoneurology, recent progress in, 835
Oxygen lack and action of cyanide on glomerular function in frog's kidney, 714
want and intracranial pressure, 673

P

Paraldehyde, blood and urine of dogs following, 329
Park, F. R., and Herr, B. S., *see* Cutler, J. W., 734
Parker, F., Jr., and Jackson, H., Jr., *see* Turner, J. C., 27
Parkinsonism, chronic encephalitic, high-dosage atropine therapy in, 809
Pathological changes produced by gastrectomy in young swine, 717
Pathology, experimental, of ergotism; some newer ergot derivatives, 452
Pellagra and myxedema, coexistence of, in same patient; 2 case reports, 618
Peptic ulcer, control of gastric acidity in, by alkalinized powdered skimmed milk tablets, 676
Periarteritis nodosa, case report confirmed by necropsy, 651
Peripheral nerve palsies and electrocardiographic changes in toxic diphtheria, 301
nerves, tumors of, in fish, 278
Pernicious anemia, observations on 78 cases of, with special reference to weight changes, 150
optic atrophy in, 633
Petri, S., Nørgaard, F., and Bing, J., pathological changes produced by gastrectomy in young swine, 717
Pharmacology, human autonomic, VII, 88
Photometric studies of visual adaptation in relation to mild vitamin A deficiency in adults, 54
Physostigmine and strychnine, hyperglycemia produced by synergistic action of, 138
Pituitary, anterior, diabetogenic action of, 851
Placenta as modified arteriovenous fistula; relation to circulatory adjustments to pregnancy, 1
Pohle, F. J., Minot, G. R., and Alsted, G., *see* Heath, C. W., 281
Poisoning, chronic fluoride, composition of human bone in, 493
diazomethane; first clinical case report, 469
ivy, experimental, negative results of Rhus antigen treatment of, 361
Pregnancy, ectopic, 553
etiology of toxemias of, III, 516; IV, 723
placenta as modified arteriovenous fistula; relation to circulatory adjustments to, 1
Premature, 8-month, serial blood and bone-marrow findings of, and Roentgen ray treated chronic myeloid leukemic mother, 8
Pressor drugs and saline kidney extracts, effects of, on blood pressure and skin temperature on rabbit's ear, 427
substances from extracts of renal tissue, observations on two different, 339
Pressure analysis, investigation of blood-vessels of finger by, 850
Price, J. B., *see* Spiegel, E. A., 138
Progress, recent, in otoneurology, 835
Prontosil and related compounds, effect of, upon chemotropism of leukocytes, 574
Protein, assimilation of, by young children with nephrotic syndrome, 70
derivatives, purified, of acid-fast bacteria, intracutaneous reactions in man to, 479
Prusmack, J. J., *see* Weiss, M. M., 510
Psychiatric facilities in general hospital, 833
Pulmonary embolism, cause of death in coronary thrombosis, with reference to, 104
involvement in lymphosarcoma and lymphatic leukemia, 294
Pulse rate and blood pressure as index of emotional stability, 211
Pumpian-Mindlin, E., Rosow, H. M., *see* Jewett, S. P., 809
Purine and pyrimidine compounds, action of sodium bisulphite and sulphanilamide on, etc., 426
Pyrimidine and purine compounds, action of sodium bisulphite and sulphanilamide on, etc., 426

R

Randall, L. O., Cameron, D. E., and Looney, J. M., changes in blood lipids during insulin treatment of schizophrenia, 802

Rats, normal, glucose tolerance in, 138
Ravdin, I. S., and Frank, I. L., *see* Thompson, W. D., Jr., 426
Johnston, C. G., cancer of colon, 267
Reiner, M., and King, F. H., *see* Sohval, A. R., 608
Renal tissue, extracts of, observations on two different pressor substances from, 339
Respiratory infections and tuberculosis, influence of season and climate on mortality of white and colored population from, 501
Respiratory transport by blood of fresh water fish, 850
Reviews:
Alexander, The Collapse Therapy of Pulmonary Tuberculosis, 687
Barborka, Treatment by Diet, 698
Bard, Macleod's Physiology in Modern Medicine, 825
Barnes, Laboratory Manual of General Physiology, 260
Textbook of General Physiology, 260
Bowen, Appendicitis, 541
Braude, The Principles and Practice of Clinical Psychiatry, 107
Bucher, Die Diffusionsanalyse am Blutplasmagel, 696
Buie, Practical Proctology, 547
Bullowa, The Management of the Pneumonias, 546
Burnet, Keogh, and Lush, The Immunological Reactions of the Filterable Viruses, 829
Burrell, Recent Advances in Pulmonary Tuberculosis, 261
Campbell, Pediatric Urology, 692
Carlson and Johnson, The Machinery of the Body, 540
Cecil and Kennedy, A Text Book of Medicine, 368
Clendening, The Human Body, 263
Coughlin, Rose and Carless, Manual of Surgery, 110
Craig and Faust, Clinical Parasitology, 263
Crothers, A Pediatrician in Search of Mental Hygiene, 549
Die Werke des Hippokrates, Parts 16 and 17, 693
Donaldson, The Roentgenologist in Court, 374
Drinker, Not So Long Ago, 548
Dublin and Lotka, Twenty-five Years of Health Progress, 688
Dubois, Lane Medical Lectures: The Mechanism of Heat Loss of Temperature Regulation, 545
duNoüy, Biological Time, 372
Eagle, The Laboratory Diagnosis of Syphilis, 258
Endocrines in Theory and Practice, 690
Fairbrother, A Text-book of Medical Bacteriology, 549
Farber, The Postmortem Examination, 548
Fever Therapy, 830
Fishbein, Syphilis, 541
Flexner, Doctors on Horseback, 687
Reviews:
Franklin, A Monograph on Veins, 376
Galdston, Maternal Deaths—The Ways of Prevention, 691
Gantt, Russian Medicine, 542
Gask and Ross, Surgery of the Sympathetic Nervous System, 691
Gatenby and Painter, The Micromotist's Vade-Medum (Bolles Lee), 375
Gonzales, Vance and Helpern, Legal Medicine and Toxicology, 825
Grimsdale and Brewerton, A Textbook of Ophthalmic Operations, 695
Grinker, Neurology, 824
Hamman, International Clinics, Vol. IV. Forty-seventh Series, December, 1937, 550
Harris, Vitamins in Theory and Practice, 548
Hawk and Bergeim, Practical Physiological Chemistry, 696
Hawley, The Kinesiology of Corrective Exercise, 111
Heilbrunn, An Outline of General Physiology, 370
Holmes, A Dissertation on Acute Pericarditis, 695
Huhner, The Diagnosis and Treatment of Sexual Disorders in the Male and Female Including Sterility and Impotence, 550
Joslin, A Diabetic Manual for the Mutual Use of Doctor and Patient, 263
Koch, Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung, 372
and Standler, Archiv für Kreislaufforschung, Band 1, Hefts 1–6, 7–8, 829
Kolmer and Boerner, Approved Laboratory Technic, 826
Ling, Recent Advances in Industrial Hygiene and Medicine, 539
London, Mental Therapy, 689
Löwenstein, Der Psychische Restitutionseffekt, 546
Loewenburg, Clinical Endocrinology, 367
MacKinney, Early Medieval Medicine, 374
Malloch, Short Years, 691
Margolis, Clinical Reviews of the Pittsburgh Diagnostic Clinic, 259
Markowitz, Textbook of Experimental Surgery, 828
Means, The Thyroid and Its Diseases, 110
Menninger, Man Against Himself, 697
The Human Mind, 373
Merritt and Fremont-Smith, The Cerebrospinal Fluid, 545
Meyer, An Analysis of the De Generatione Animalium of William Harvey, 694
Morgan, A Discourse Upon the Institution of Medical Schools in America, 370
Morris, Maternity and Post-operative Exercises, 109
Nissen, Chirurgische Indikationen, 109
Ormsby, A Practical Treatise on Diseases of the Skin, 786

Reviews:
Osgood and Ashworth, Atlas of Hematology, 108
Page, Chemistry of the Brain, 695
Petersen, The Patient and the Weather, Vol. 4, Pt. 2, 261
Plant, Personality and the Cultural Pattern, 369
Poynton and Schlesinger, Recent Advances in the Study of Rheumatism, 543
Price, A Textbook of the Practice of Medicine, 369
Puder, Condition Satisfactory, 262
Rice, Injection Treatment of Hernia, 107
Roesler, Clinical Roentgenology of the Cardiovascular System, 261
Rolleston *et al.*, The British Encyclopædia of Medical Practice, Vols. 5 and 6, 826
Rowe, Clinical Allergy, 697
Rudolph, Allergy, 373
Saxl, Pediatric Dietetics, 367
Schulten, Die Sternalpunktion als Diagnostische Methode, 371
Schweitzer, Die Irradiation autonomer Reflexe, 830
Shearer, Manual of Human Dissection, 827
Shwartzman, Phenomenon of Local Tissue Reactivity and Its Immunological, Pathological and Clinical Significance, 539
Sigerist, Socialized Medicine in the Soviet Union, 690
Sobotka, Physiological Chemistry of the Bile, 692
Solomon, The Traffic in Health, 108
Strecker and Chambers, Alcohol: One Man's Meat, 829
Stutterheim, Eyestrain and Convergence, 375
Thacher, A Brief Rule to Guide the Common-people of New-England, 370
Tuft, Clinical Allergy, 371
Wangensteen, The Therapeutic Problem in Bowel Obstructions, 375
Weck, Heilkunde und Volkstum auf Bali, 260
Weinzirl, General Hygiene and Preventive Medicine, 257
Weiss, Die Homoöpathische Behandlung der Augenkrankheiten, 373
Practical Talks on Kidney Disease, 111
Welch, Adaptation in Pathological Processes, 370
Whitby and Britton, Disorders of the Blood, 109
Wolf, The Physician's Business, 827
Zabriskie, *et al.*, Tumors of the Nervous System, 374
Reznikoff, P., etiologic importance of fatigue and prognostic significance of monocytosis in neutropenia (agranulocytosis), 627
"Rheumatic heart disease, potential," and "rheumatic mitral insufficiency," prognosis in, 764
manifestations, relationship of Sydenham's chorea to, 656
Rhus antigen treatment of experimental ivy poisoning, negative results of, 361
Richards, A. N., *see* Beck, L. V., 714
Rosenberg, J., *see* Rosenberg, L., 682
Rosenberg, L., and Rosenberg, J., subcutaneous emphysema complicating bronchial asthma; case report and 17 previous ones, 682
Rosow, H. M., and Pumpian-Mindlin, E., *see* Jewett, S. P., 809
Rubber sheaths as venereal disease prophylactics; quality and technique, 155; note on, 852
Rucker, C. W., treatment of tobacco alcohol amblyopia, 274

S

Saline kidney extracts and pressor drugs, effects of, on blood pressure and skin temperature of rabbit's ear, 427
Sandler, B. P., periarteritis nodosa; case report confirmed by necropsy, 651
Sandusky, W. R., *see* Holman, C., 220
Schizoprenia, changes in blood lipids during insulin treatment of, 802
Schmidt, C. F., and Hendrix, J. P., action of chemical substances on cerebral circulation, 427
Schwab, R. M., and Semrad, E. V., *see* Thomas, J. M., 820
Scott, G. H., and McMillen, J. H., spectrographic determination of lead in blood from normal human subjects, 622
Season and climate, influence of, on mortality of white and colored population from tuberculosis and respiratory infections, 501
Sedimentometer; photographic recorder of suspension stability of erythrocyte, 729
Semrad, E. V., and Schwab, R. M., *see* Thomas, J. M., 820
Sensitivity, acquired, to cinchophen; 6 case reports and review, 473
Sensitized calves, character of leukocytic response to tuberculin in, 20
Serial blood and bone-marrow findings of 8-month premature, and Roentgen ray treated chronic, myeloid leukemic mother, 8
Sevag, M. G., *see* Czarnetzky, E. J., 426
Shapiro, S. L., recent progress in otoneurology, 835
Shay, H., Gershon-Cohen, J., and Fels, S. S., rôle of upper small intestine in control of gastric secretion, etc., 139
Sheaths, rubber, as venereal disease prophylactics; quality and technique, 155; note on, 852
Siegel, A. E., tuberculosis in childhood, 129

Skin inflammation (dermatitis), carbohydrate and water metabolism and vitamins in, 562
Smith, L. W., and Eggleston, C., *see* Burkhardt, E. A., 301
Snow, J. S., *see* Wile, U. J., 240
Sodeman, W. A., recent concepts in pathogenesis of diastolic hypertension, 115
Sodium bisulphite and sulphanilamide, action of, on purine and pyrimidine compounds, etc., 426
Sohval, A. R., King, F. H., and Reiner, M., creatine tolerance test in differential diagnosis of Graves' disease, etc., 608
Soley, M. H., *see* Anderson, H. H., 313
Sompayrac, L. McC., negative results of Rhus antigen treatment of experimental ivy poisoning, 361
Southworth, H., and Flake, C. G., blood cultures after tonsillectomy, 667
Sparkman, D., and Montgomery, H., *see* Landis, E. M., 427
Spectrographic determination of lead in blood from normal human subjects, 622
Spiegel, E. A., and Price, J. B., conduction of labyrinthine impulses to cerebral cortex, 138
Splenogenic controlling of cell emission from bone marrow and tuberculous splenomegaly, study of, 32
Splenomegaly, tuberculous, and splenogenic controlling of cell emission from bone marrow, study of, 32
Stasney, J., and Feldman, W. H., character of leukocytic response to tuberculin in sensitized calves, 20
Sterility of alcohol, 358
Stiehm, R. H., and Getz, H. R., *see* McCarter, J., 479
Stokes, J. H., Beerman, H., and Ingraham, N. R., Jr., carbohydrate and water metabolism and vitamins in skin inflammation (dermatitis), 562
Stomach, cancer of, macrocytic anemia in, apparently due to lack of intrinsic factor, 17
influence of filling, on colon motility and defecation in dog, 230
Strauss, M. B., etiology of toxemias of pregnancy, III, 516; IV, 723
Streptococci, hemolytic, invasive properties of, and their control by sulphanilamide, 577
Streptococcic meningitis, experimental, sulphanilamide in, 575
Strychnine and physostigmine hyperglycemia produced by synergistic action of, 138
Sugg, E. S., acquired sensitivity to cinchophen; 6 case reports and review, 473
Sulphanilamide and similar compounds in chemotherapy, 379
Sulphanilamide experience with, in meningitis, 175
in experimental streptococcic meningitis, 575
invasive properties of hemolytic streptococci and their control by, 577
sodium bisulphite, action of, on purine and pyrimidine compounds, etc., 426
transient nodal rhythm following use of, 771
treatment of beta hemolytic streptococcic infection, 163
use of, in treatment of various infections, 701
Sunderman, F. W., Connor, R., and Fields, H., diazomethane poisoning; first clinical case report, 469
Supravital technique, studies of Gaucher cells by, 144
Sutherland, C. G., chronic gastritis, 708
Sutton, L. P., and Dodge, K. G., relationship of Sydenham's chorea to other rheumatic manifestations, 656
Swine, young, pathological changes produced by gastrectomy in, 717
Sydenham's chorea, basal metabolic rate of children with; 42 patients, 519
relationship of, to other rheumatic manifestations, 656
Syphilis, occult cardiovascular, 240

T

Templeton, R. D., *see* Galapeaux, E. A., 230
Thienes, C. H., and Butt, E. M., chronic circulatory effects of tobacco and nicotine, 522
Thiobarbiturates, cardiac arrhythmia characteristic effect of, as influenced by changes in arterial blood pressure, 575
Thomas, J. M., Semrad, E. V., and Schwab, R. M., studies of blood proteins in delirium tremens, 820
Thompson, J. W., *see* Michelsen, J., 673
Thompson, W. D., Jr., Ravdin, I. S., and Frank, I. L., use of lyophile plasma in correcting hypoproteinemia and preventing wound disruption, 426
Thorium dioxide sol, histopathologic study of tissues of 65 patients injected with, for hepatosplenography, 198
Thyroid and liver, effects of carotenemia on function of, 313
Tobacco alcohol amblyopia, treatment of, 274
and nicotine, chronic circulatory effects of, 522
Tonsillectomy, blood cultures after, 667
Toxemias of pregnancy, etiology of, III, 516; IV, 723

Toxicology of cyanide, 182
Tuberculin in sensitized calves, character of leukocytic response to, 20
Tuberculosis, active, urinary output of vitamin C in, in children, 362
and respiratory infections, influence of season and climate on mortality of white and colored population from, 501
in childhood, 129
Tuberculous splenomegaly and splenogenic controlling of cell emission from bone marrow, study of, 32
Tumors of peripheral nerves in fish, 278
Turner, J. C., Jackson, H., Jr., and Parker, F., Jr., etiologic relation of eosinophil to Gordon phenomenon in Hodgkin's disease, 27
Twin sisters, homologous, further note on carcinoma of breast in one of, 366
Typhoid meningitis, purulent, with recovery; case report, 497

U

Ulcer, peptic, control of gastric acidity in, by alkalinized powdered skimmed milk tablets, 676
Urinary output of vitamin C in active tuberculosis in children, 362
Urine and blood of dogs following paraldehyde, 329
Uterus and bowel, effect of benzedrine sulphate on, 445

V

Van Cleave, C. D., effect of dead optic vesicle on explanted gastrular ectoderm, 574
Venereal disease prophylactics, rubber sheaths as; quality and technique, 155; note on, 852
Venous pressure, normal, as determined by direct method, 751
Visual adaptation, photometric studies of, in relation to mild vitamin A deficiency in adults, 54
Vitamin A deficiency in adults, mild, photometric studies of visual adaptation in relation to, 54
specific dermatoses due to, 644
C, urinary output of, in active tuberculosis in children, 362
Vitamins, carbohydrate and water metabolism and, in skin inflammation (dermatitis), 562

W

Walker, A. M., experiments on water diuresis, 715
Wartman, W. B., *see* Moritz, A. R., 65
Water diuresis, experiments on, 715
metabolism and carbohydrate and vitamins in skin inflammation (dermatitis), 562
Weight changes, observations on 78 cases of pernicious anemia with special reference to, 150
Weiss, M. M., and Prusmack, J. J., essential hypertension in negro, 510
Whipple liver fraction (secondary anemia fraction), clinical observations on, 287
Whitmore, E. R., *see* Yater, W. M., 198
Wile, U. J., and Snow, J. S., occult cardiovascular syphilis, 240
Williams, J. R., Jr., Harrison, T. R., and Mason, M. F., observations on two different pressor substances from extracts of renal tissue, 339
Wolff, W. A., and Kerr, E. G., composition of human bone in chronic fluoride poisoning, 493
Wosika, P. H., control of gastric acidity in peptic ulcer by alkalinized powdered skimmed milk tablets, 676
Wound disruption, preventing, and correcting hypoproteinemia, use of lyophile plasma in, 426

X

Xanthoma diabeticorum, case of, associated with diabetes mellitus and acromegaly, 50

Y

Yater, W. M., and Whitmore, E. R., histopathologic study of tissues of 65 patients injected with thorium dioxide sol for hepatosplenography, 198
Yawger, N. S., marihuana; our new addiction, 351
Youmans, J. B., and Corlette, M. B., specific dermatoses due to vitamin A deficiency, 644
Frank, H., and Corlette, M. G., *see* Corlette, M. B., 54

Z

Zetzel, L., and Glenn, P. M., *see* Abbott, W. O., 279
Zinc content, effect of, upon action of insulins, 234